Constructs underlying mild cognitive impairment of relevance to low and middle income countries

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CONSTRUCTS UNDERLYING MILD COGNITIVE IMPAIRMENT OF RELEVANCE TO LOW AND MIDDLE INCOME COUNTRIES

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AUTHOR'S DECLARATION

I hereby declare that I am the author of this thesis. The study design and data collection was done for the 10/66 Dementia Research Group under direction of Professor Martin Prince.

I am member as a Principal Investigator for Mexico of this group, with whom I have participate as such since 12 years ago in all the phases of the10/66 program including: the collection and data handling in all its phases (the pilot and the evaluation instruments validation study, the prevalence and incidence studies).

The 10/66 Dementia Research group knows and accepts the use of its date base with the purpose of the elaboration of the thesis for this PhD study.

All subsequent hypotheses and analyses for this PhD thesis were developed and carried out by the author and were specifically directed on for the purpose of this thesis project.

This thesis has been written by the author along all the PhD period under the supervision of Professor Robert Stewart as first supervisor, and in the first stages of the same one with the additional participation of Dr. Emiliano Albanese as second supervisor,

This is a true copy and includes any revisions requested by examiners.

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ABSTRACT

Background: Numbers of older people are increasing rapidly in most low and middle-income countries and there is a pressing need for adequate information on dementia and cognitive disorders in these regions. Mild cognitive impairment is increasingly recognized as an important 'transition' prior to dementia onset, but is poorly understood outside Western settings, as are key constructs underlying this concept: namely, subjective memory complaints, informant-reported memory deficits and the relationship between cognition and disability.

Methods: Data were analysed in relation to these questions from a series of catchment area surveys of older people carried out following identical methodologies in Cuba, Mexico, Dominican Republic, Peru, Venezuela, India and China, involving over 15,000 participating residents aged 65 years and over. Measurements had been rigorously assessed for cross-cultural applicability and were identically administered.

Results: Normative data for cognitive function are described and compared, followed by the prevalence of amnestic mild cognitive impairment. Substantial variations were found between sites in the prevalence of subjective memory complaints and informant-reported memory deficits, and in their associations with dementia, and with cognitive function in participants without dementia. Variation was also found in the association between cognitive function and informant-reported disability in participants. For example, subjective memory complaints in China were relatively rare but much more strongly associated with dementia and/or cognitive function than in other sites.

Conclusions: The high level of between-site variability in the associations in question suggests that mild cognitive impairment as a construct is strongly influenced by cultural factors which need to be taken into account when interpreting it or applying it in healthcare.

252 words

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I. - DEMOGRAPHIC AGEING IN LOW AND MIDDLE INCOME SETTINGS

I.1 Worldwide demographical aging

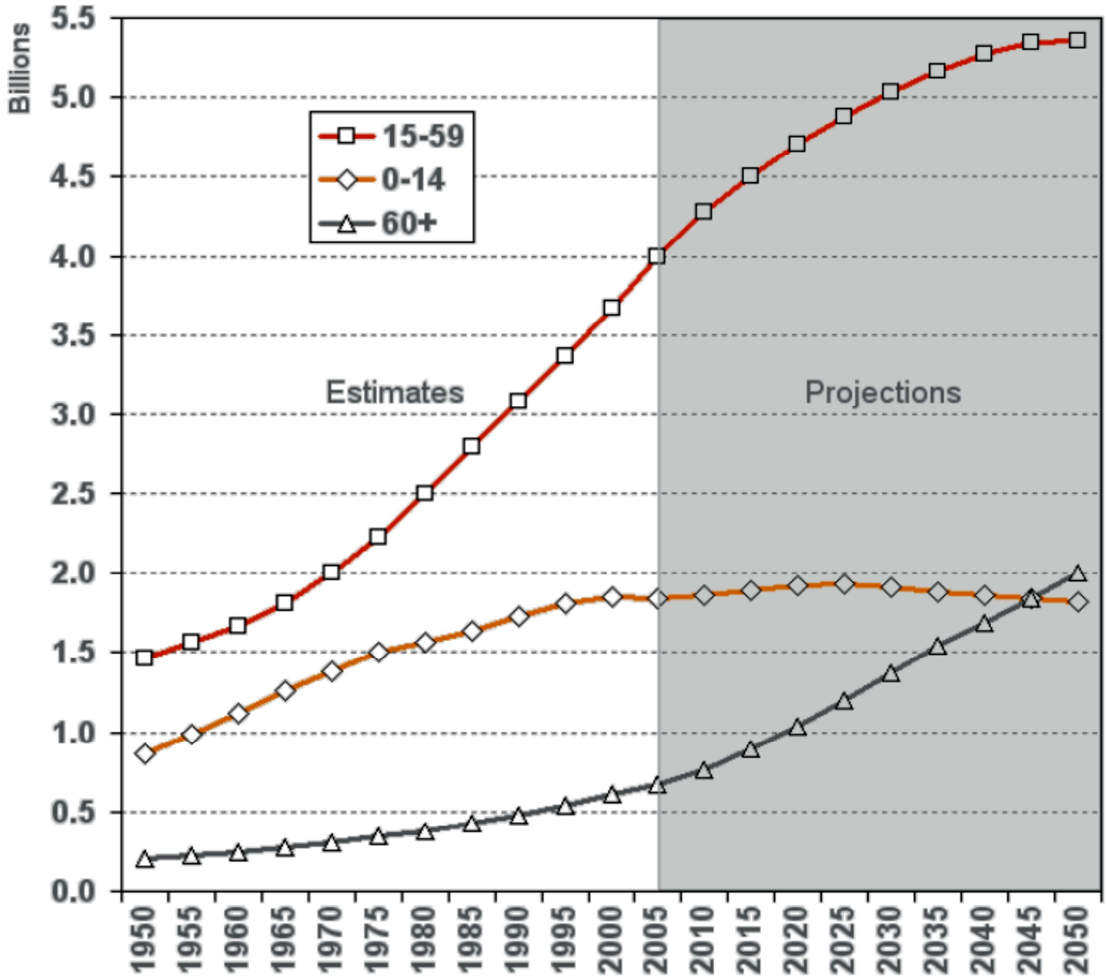
Population ageing has been one of the most important demographic events of the twentieth century and is likely to persist in the twenty first, with profound impacts on a broad range of economic, political and social outcomes. Although this demographic change began in developed countries, many low and middle-income countries face dramatic and rapid population ageing.

From the 1950´s to the year 2000, the global population aged 60 years or over increased about three-fold, from 205 million to 606 million, and for the first half of the current century it is projected that this will expand again more than three-fold to reach nearly 2 billion in 2050. By the year 2000, 1 person in every 10 was age 60 years or older and by the year 2050 it is projected that a 1 in 5 proportion will be attained. Currently, the average annual growth rate of persons aged 80 or over is 3.8 per cent: twice as high as the growth rate of 60-79 year olds (1.9 per cent). At the moment, women comprise a significant majority of the ageing population because their life expectancy is greater than men's, and in the year 2000 the world's population aged 60 or over comprised 81 males per hundred females. However, the expected trend for the next half-century is an equalizing of this sex ratio because of a faster growth in life expectancy among men than women, particularly in more developed regions. In 2050, the global number of men per hundred women is projected to rise to 85 at ages 60 over, to 81 at ages 65 or over, and to 61 at ages 80 or over (U.N., 2002).

According to the 2006 Revision of the World Population Prospect, by 2045 the number of older persons in the world (those aged 60 years or over) will likely surpass, for the first

time in the history, the number of children (i.e., persons under age 15). This crossover is the consequence of long term reductions in fertility and mortality that are leading to the steady ageing of the world population (Figure I.1) (WHO, 2006).

Figure I.1 World population by age groups, 1950-2050



Source: World Population Prospects: The (U.N., 2006) Revision. Fact Sheet, Series A. Population Division of the Department of Economic and Social Affairs of the United Nations Secretariat Ed. New York: United Nations

Sustained reductions of fertility slow down population growth and produce eventual reductions in the number of births and hence in the proportion of children in the population.

Furthermore, increases in longevity accelerate the growth of the proportion of older persons more than those of young people or adults. (WHO, 2006)

Demographic transition is a model used to describe characteristics of national or regional population changes, with several stages. In the first of these, birth and mortality rates are high, which produces low population growth. In the second (truly transitional) stage, a reduction in mortality and a continuing high birth rate lead to an increase in population growth rates. In the third phase, known as advanced transition, mortality rates have fallen and birth rates decline too, which results in diminishing rates of population growth. In the post-transition phase, birth rates drop below the level of mortality rates, thus resulting in extremely low or even negative natural population growth (Chackiel, 2004 , Schkolnik, 2007, Villa and González, 2004)

Worldwide life expectancy at birth has increased about 20 years since 1950, to its current level of 68 years and is projected to rise to 76 years by 2050 (U.N., 2009). By 2050 20% of the older population will be aged 80 years or over. The change observed in the shape of survival curves, which has been termed *rectanglearisation*, shows that more and more individuals survive to very old age, and all of them die in a very narrow time window (Ferrucci et al., 2008).

In order to provide context for this thesis, whose research questions particularly concern age-related conditions, brief summaries follow on the position of high income countries, from where most current research evidence derives, followed by a generic description of

low and middle income counties and then more specific illustrations from Latin America and the Caribbean as an example of a region with rapid demographic transformation.

I.2 Population Ageing in High Income Countries

In high-income countries, fertility rates have been falling since the 1950s reaching a minimum of 1.64 children per woman in 2010. Furthermore, infant mortality has reached the lowest rate in history: five per 1000 live births in Japan, and less than 10 per 1000 in most other HIC. Mortality rates are continuing to fall in these settings for both sexes at both extreme ages. The current life expectancy at birth of 77 years is projected to rise to 83 years by 2050.(U.N., 2009). Population growth in high-income countries fell from 1.21% per year in the 1950s to just 0.34% between 2000 and 2010. UN estimates suggest that the rate of growth in these countries is going to continue fall, reaching -0.07% by 2050 (U.N., 2009)

In high-income countries the oldest population already accounts for 22% of the total population, and is estimated to reach 33% by 2050. In 2010, numbers in the older population surpassed those of the children (22% vs. 17%), and in 2050 it is projected that 60 and more years old people will account for 33% and children 15% of the total population of high income countries (U.N., 2009)

I.3 Population Ageing in Low and Middle Income Countries

When information related to older population is consulted, inconsistencies about age ranges are found. Most developed world countries have accepted a chronological age of 65 years and above as a definition of 'the elderly' or older people. However, this merely reflects the age of pension receipt in some countries and, like many westernized concepts, has very

limited relevance for low and middle income countries where retirement is a more fluid or non-existent concept. At the moment, the UN agreed cut-off is 60+ years to refer to the older population.

In many less developed regions of the world, the older population is growing at a much faster rate than has been observed in developed nations. In the last fifty years the rates of increase have tended to decline in the more developed regions and to increase in less developed regions. Currently in more developed regions the average annual growth rate of the population of persons 60 years or over is 0.9%, while less developed regions have an average of 2.5%. Furthermore, 66% of the increase of elderly population in the last half century has occurred in less developed regions compared to 34% in more developed regions. Gender distributions in the elderly population are not the same as those observed in developed countries; in less developed regions older women do not generally outnumber older men to the same extent as in developed countries and gender differences in life expectancy are generally much smaller.

In contrast to developed countries, in less developed regions there are high proportions of older people remaining in the labour force because of less comprehensive pensions and support systems. By 2000 the labour force participation of the population aged 65 and over was 26% and in more developed regions 8% (U.N., 2002).

Despite the improved life expectancy underlying these demographic trends, lack of education remains an

Issue, which has not been substantially addressed. Although illiteracy among older people has declined in the last decades, particularly among males, it still remains high in less developed regions. In 2000, 56 per cent of people aged 60 or over in the world were estimated to be illiterate (Kinsella and Wan, 2009).

For the coming half-century, mixed trends are projected although in most countries the number and proportion of woman will increase. The evidence on which the projections are based suggests a somewhat faster growth in life expectancy among men than among women, particularly in the more developed regions. In 2050, the global number of men per hundred women is projected to rise to 85 at ages 60 or over, to 81 at ages 65 or over, and to 61 at ages 80 or over. (U.N., 2002).

A particularly rapid increase in the population aged 80 years or over is expected which means that demographic ageing in less developed regions will be characterized by people in more advanced old age.

I.4 Demographic transition illustrated in Latin America and the Caribbean

As described above, the initial stage of the demographic transition process is characterized by a change from high to low mortality rates and, subsequently, a steady decline in fertility, until both variables reach low levels (Schkolnik, 2007, Villa, 2005, Chackiel, 2004). This model was originally formulated to interpret the sociodemographic transformation that took place in European countries from the mid-eighteenth to the mid-twentieth century (Villa and González, 2004) but offers a good fit, albeit with certain differences, with the process

undergone by Latin America and the Caribbean in more recent times, taking place much more rapidly over less than 50 years. (ECLAC, 2004).

Over this period, regional mortality for Latin America and the Caribbean has dropped by 10 percentage points to give a gross mortality rate of 6.1 deaths for every 1,000 inhabitants between 2000 and 2005 (Huenchuan, 2009).

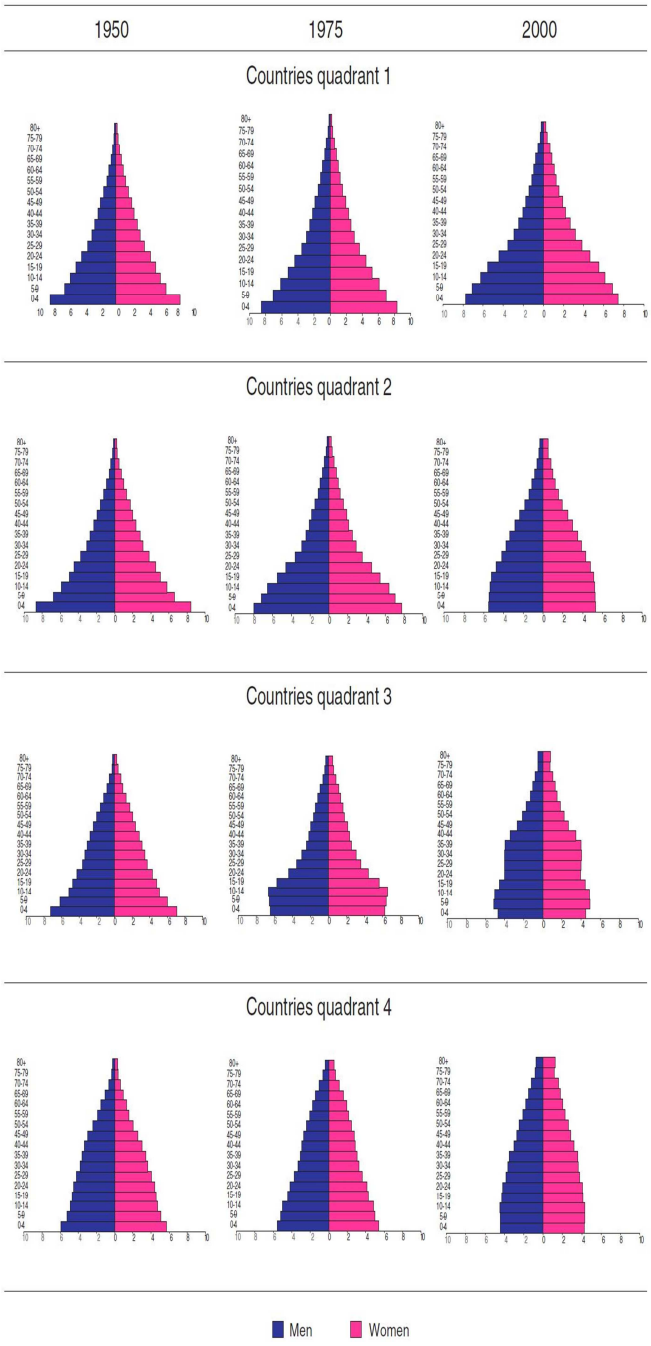
Female life expectancy is longer than men throughout the region, due among other things to reductions in deaths during pregnancy and childbirth, causes of death which are usually controlled more successfully than those that prevail among men, such as cardiovascular disease, external causes (including violence) and certain cancers (ECLAC, 2004, CELADE, 2006).

Most countries in Asia or in Latin America and the Caribbean find themselves in the second stage of the transition where the population of working age (from 15 to 59 years) is still growing as a proportion of the whole population. By 2050 the median age is projected to increase by over 12 years in 32 of the 37 countries in this region, and by 2050 21 countries in the region are expected to have a median age higher than 40, including Brazil and México (Huenchuan, 2009).

The components of demographic change (fertility and mortality) have an impact both on the growth of the population in numbers and on its age structure. As demographic transition progresses and mortality and especially fertility decline, the population gradually ages (Chackiel, 2004 , ECLAC, 2004, Villa and González, 2004). This transition is best illustrated graphically, where the conventional outline of the age and gender structure of the

population, a pyramid with a wide base and narrow tip illustrating the preponderance of children and rarity of older age groups, first morphs into a more rectangular shape and subsequently inverts its initial form with the top wider than the base (Chesnais, 1990) Changing regional population structures in the latter half of the 20th Century are illustrated in Figure I.2.

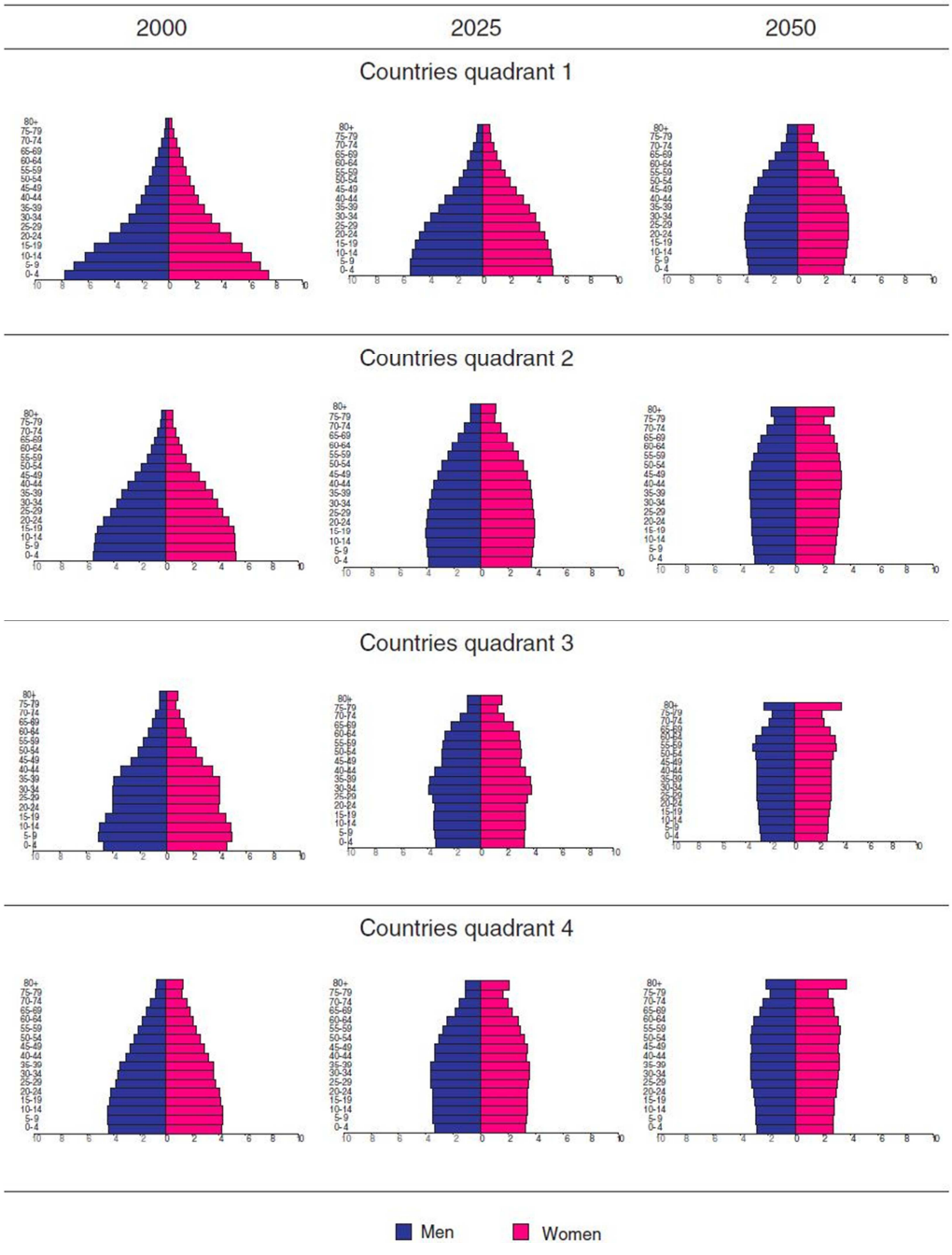
Figure I.2 Latin America and the Caribbean: average age and sex structures of the population, by stage of demographic transition of the region's countries, 1950-2000.



Modified from: Sandra Huenchuan ed.(2009), *Envejecimiento, derechos humanos y políticas públicas*, Libros de la CEPAL Nº 100 (LC/G.2389-P), Santiago de Chile, CEPAL (Economic Commission for Latin America and the Caribbean)

According to a recent review of population projections conducted by the Latin American and Caribbean Demographic Centre (CELADE) - Population Division of ECLAC, changes in the pyramid structure will have become steadily more drastic by 2025, when children under 15 will represent only 23% of the population in this region and older adults will make up almost 15%. The larger cohorts born in previous decades also will be progressing through adulthood and broadening the central bands of the pyramid that will continue for decades to come. The new age profile is forming a pyramid with a narrower base and wider central sections, corresponding to an older population structure. Around 19% of the population in the most transitionally advanced countries will be aged 60 or over, while the percentage of children under age 15 will drop to 20%. The least transitionally advanced countries will have a smaller proportion of older adults (8%), which will slowly increase in line with the decrease in the population aged 0 to 14 years (32%). By 2050, the classic pyramid structure will be completely replaced by a rectangular shape where each age group represents practically the same proportion of the population. Children under the age of 15 will represent 18% of the total regional population, and older adults will represent 24%. Countries that were already displaying population ageing in 2000 will have the highest proportion of older people (27%), while the least advanced countries in the transition will have considerably increased their proportion of people aged 60 and above to 15% of the total. Projected trends are illustrated in Figure I.3.

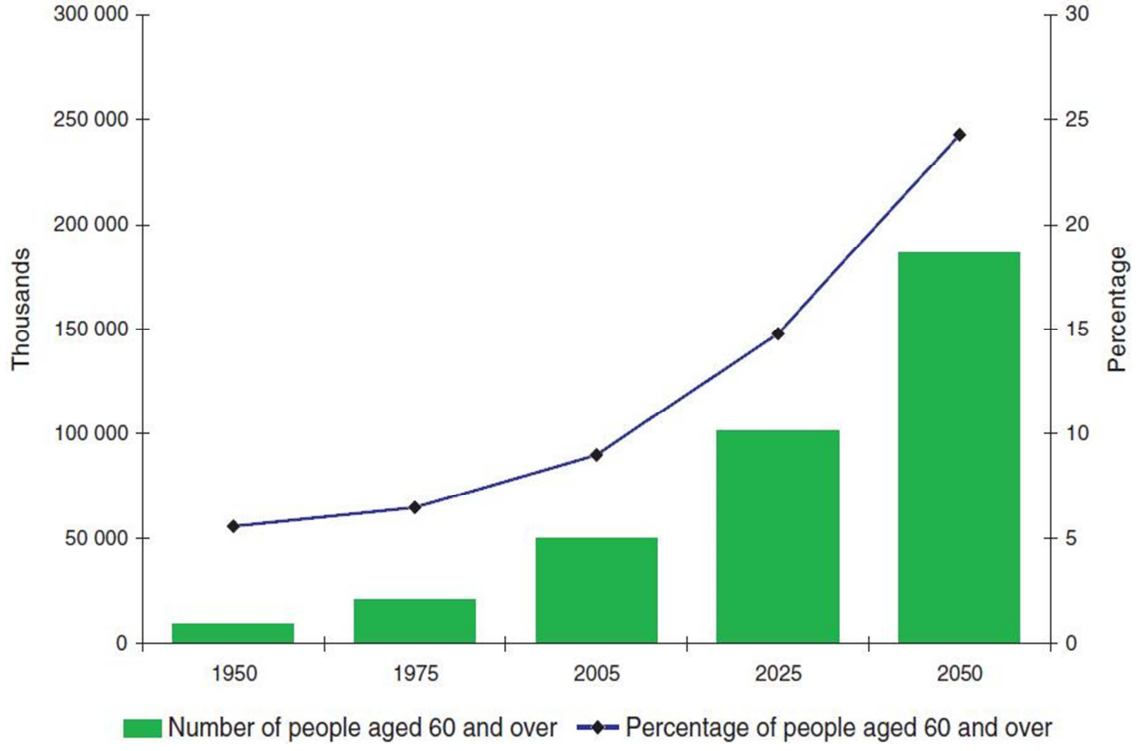
Figure I.3 Latin America and the Caribbean: average age and sex structures of the population, by stage of demographic transition of the region's countries, 2000-2050



Modified from: Sandra Huenchuan ed. (2009), *Envejecimiento, derechos humanos y políticas públicas*, Libros de la CEPAL Nº 100 (LC/G.2389-P), Santiago de Chile, CEPAL (Economic Commission for Latin America and the Caribbean)

As a result of demographic transition, the population of Latin America and Caribbean is gradually but inexorably ageing. The next few decades will see steady increases in both the proportion and the absolute number of people aged 60 and over. In absolute terms, the number of people aged 60 and over (currently 41 million) is expected to grow by 57 million between 2000 and 2025, and by 86 million between 2025 and 2050. This population group is growing at a faster pace than other younger groups (average annual growth rate of 3.5%). The rate of change within this age group will be between three and five times higher than among the total population in the periods 2000-2025 and 2025-2050. As a result, the proportion of people aged 60 and over in the total population will quadruple between 2000 and 2050, such that one in every four people in Latin America and the Caribbean will be an older adult in the year 2050 (Figure I.4).

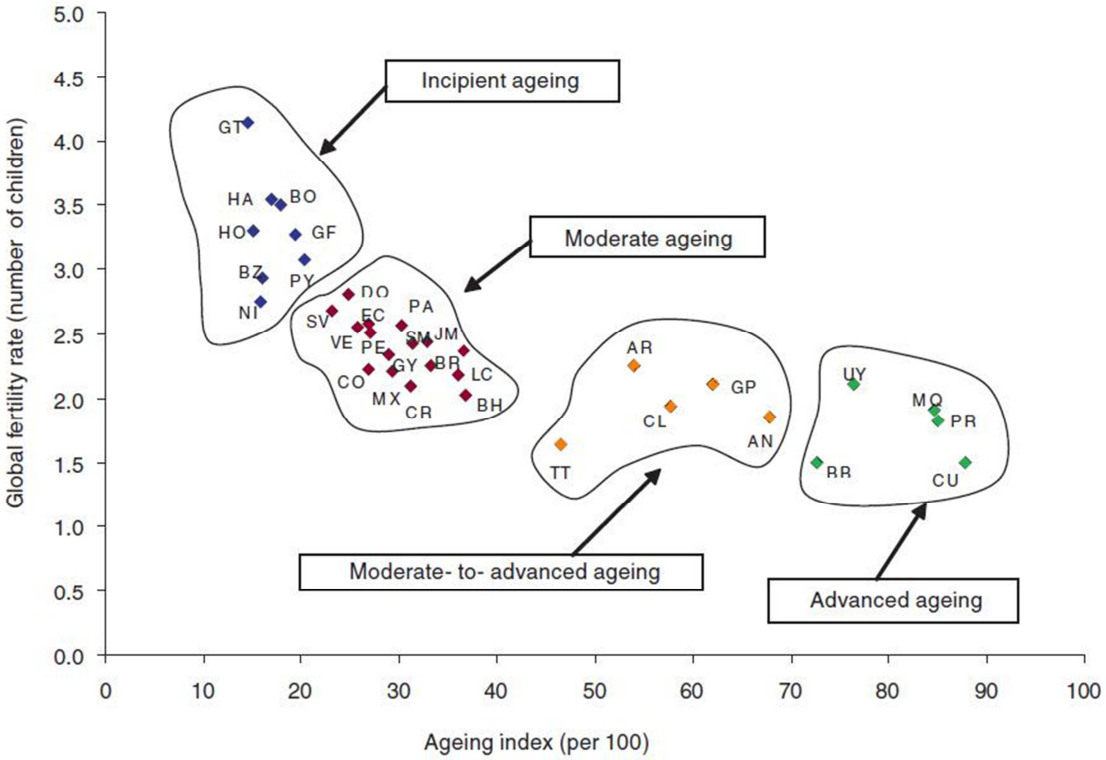
Figure I.4 Latin America and the Caribbean: population aged 60 and over, 1950-2050 (thousands and percentages)



Modified from: Sandra Huenchuan ed. (2009), *Envejecimiento, derechos humanos y políticas públicas*, Libros de la CEPAL Nº 100 (LC/G.2389-P), Santiago de Chile, CEPAL (Economic Commission for Latin America and the Caribbean)

The fact that countries are at various stages of demographic transition means that the ageing process is different in each one. In order to classify this region's countries according to their stage in the process of population ageing, the global fertility rate was combined with the ageing index (ratio between the number of people aged 60 and over and the number of children under the age of 15) for each country in the year 2007 (Figure I.5).

Figure I.5 Latin America and the Caribbean: position of countries according to stage of population ageing process, 2007



GT= Guatemala, **HA**= Haiti, **BO**= Bolivia, **HN**= Honduras, **GF**= French Guyana, **BZ**= Belize, **PY**= Paraguay, **NI**= Nicaragua, **DO**= Dominican Republic, **PA**= Panama, **EC**= Ecuador, **SV**= El Salvador, **VE**= Bolivarian Republic of Venezuela, **PE**= Peru, **SM**= San Marino **JM**= Jamaica, **CO**= Colombia, **GY**= Guyana , **BR**= Brasil, **LC**= Saint Lucia , **MX**= Mexico, **CR**= Costa Rica, **BH**= Bahrain, **AR**= Argenitna, **CL**= Chile, **TT**= Trinidad y Tobago, **GP**= Guadeloupe, **AN**= Netherlands Antilles, **UY**= Uruguay, **MO**= Macao, **PR**= Puerto Rico, **CU**= Cuba, **BB**= Barbados

Modified from: Sandra Huenchuan ed. (2009), *Envejecimiento, derechos humanos y políticas públicas*, Libros de la CEPAL Nº 100 (LC/G.2389-P), Santiago de Chile, CEPAL (Economic Commission for Latin America and the Caribbean)

This figure shows that there are four distinct groups of countries. The first group has relatively high levels of fertility and a relatively low ageing index, and can be viewed as being at the incipient stage of the demographic transition process (eight countries). Three more groups follow this one, at increasingly advanced stages of demographic transition. The figure illustrates the heterogeneity in transition stages across the region and highlights the importance of considering countries' specific situations with respect to age-related morbidity rather than assuming a single 'low and middle-income countries' entity.

I.5 Conclusions

In Latin America and the Caribbean, the rapid pace of demographic transition has meant that there has been less time to make the necessary socio-economic and institutional adjustments to adapt to the emerging demographic situation – for example, slower and more volatile economic and social development. Over the next 50 years, older age groups themselves will age rapidly, with most dramatic expansion in those aged 75 and over (expected to remain above that of the population aged 60 and over during the period 1950-2050). Although low and middle income countries share some similarities in demographic transitions, there is substantial heterogeneity: particularly in the pace of change (U.N., 2009).

For example, in Latin America and the Caribbean life expectancy has been increasing steadily and has now reached 70 for men and 76 for women. India and China on the other hand have experienced more dramatic increasing from only 38 years in the 1950s to a current level of 63 years in India, and from 41 to 73 years in China (U.N., 2009). However, in the poorest countries (mostly in sub-Saharan Africa) life expectancy remains only 56 years, with projections for a more modest increase to 69 years by the mid-21st century.

II. - HEALTH TRANSITIONS IN LOW AND MIDDLE INCOME COUNTRIES

II.1 Worldwide health transition

Declining fertility with increasing life expectancies has led to a marked increase in the older population globally both in relative and absolute terms. This trend has been accompanied by changes in life styles and urbanization that have contributed to an 'epidemic of chronic diseases' (Nugent, 2008). Health systems need to be prepared to respond to these evolving health scenarios and find effective strategies for the needs of older people as a rapidly growing segment of the population. The health of the ageing population will also have implications for social and economic policies (U.N., 2011)

As more people live until advanced old age, these demographic changes imply much more than just an increase in chronic morbidity. The same age-related susceptibility to chronic conditions in the same individual causes decrements in functional abilities as well as social and psychological problems that may have additional impacts on wellbeing and quality of life. Going beyond the demographic focus of counting and projecting the number of older people in the population, epidemiology has made additional contributions to our understanding of the health status and functional trajectory of older individuals.

Dementia is an age-associated condition for which prevalence and incidence rates cannot be inferred from routine administrative datasets. Instead, because of the complexities of diagnosing dementia and the fact that it is frequently unrecognized in clinical settings, agencies requiring data on the occurrence of the condition must rely on well-designed epidemiologic studies in defined geographic areas. A large review of studies on dementia incidence from around the world supported an exponential increase in dementia with age

and suggested that rates tend to be lower in East Asia than in Europe and the United States (Ferrucci et al., 2008).

The five leading causes of death: heart disease, cancer, stroke, chronic lower respiratory tract disease, and Alzheimer's disease account for 69.5% of all deaths. Alzheimer's disease, only recently included on the list of leading causes of death, was the seventh leading cause of death in older persons in 2000 and in 2003 rose to the fifth leading cause of death. This ranking is still likely a gross underestimation, and the contribution of Alzheimer's disease in the future will probably grow substantially (Ferrucci et al., 2008).

II.2 Low and Middle Income Countries health transition

The increasing prevalence of chronic disease in developing countries can be partitioned into two main trends: rising average age of the population and changing epidemiologic profile of the population.

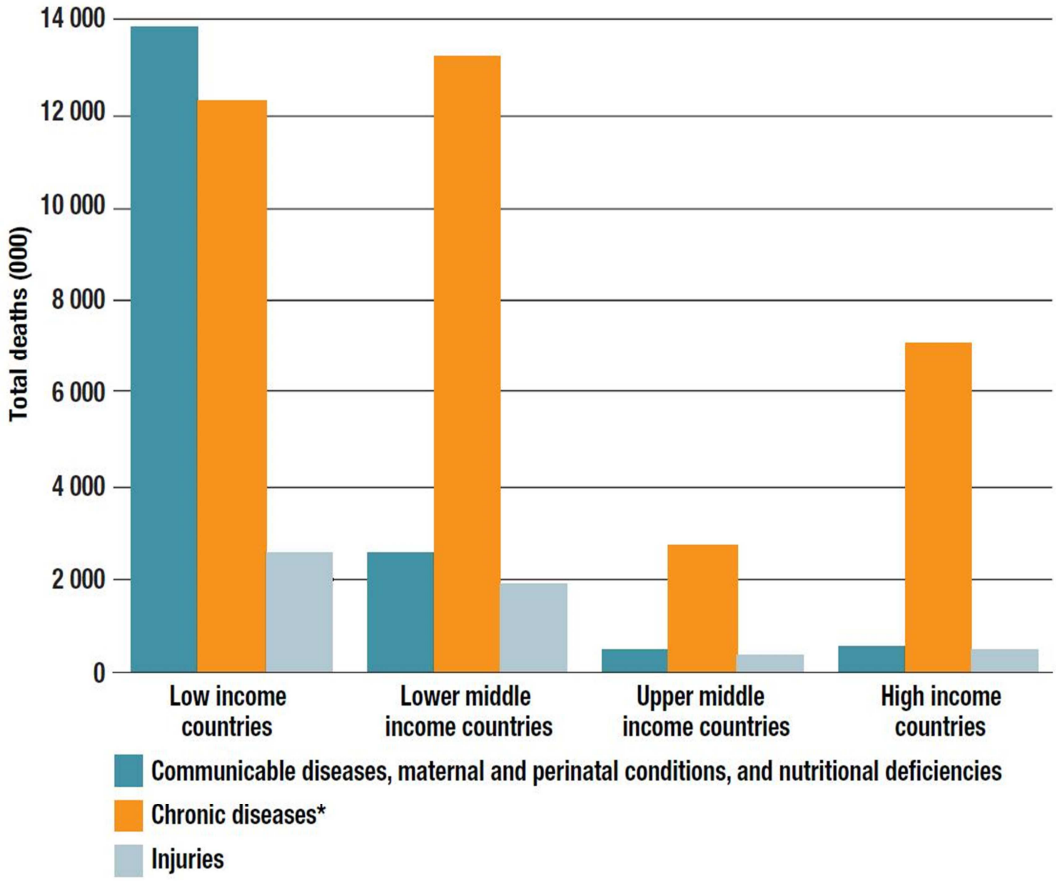
Survey data, for example, show temporal increases in the proportion of the population that is overweight or obese, a major risk factor associated with chronic diseases. These increases appear across a wide range of developing countries, but with substantial variation among those countries in the prevalence levels and rates of increase (Nugent, 2008).

In the world's developing regions people, high fat diets, smoking and sedentary lifestyles are becoming more common. Chronic non-communicable diseases (NCDs) linked to ageing – heart disease, stroke, cancer and dementia – are much more in evidence, and beginning to be recognized as a public health priority. While cancer and heart disease contribute mainly

to mortality, much of the burden of other NCDs (dementia, mental disorders, diabetes and stroke) lies in years lived with disability (Fuster and Voûte, 2005).

In low-income countries the communicable diseases, maternal and perinatal conditions and nutritional deficiencies are still causing a big number of deaths, which are decreasing in an important way in the rest of the countries (lower middle, upper middle and high income countries) so the injuries have a similar pattern even but with a very lower number of deaths; meanwhile in the other hand chronic diseases represent the most important cause of death for the most of the countries with the exception of the LIC where they are increasing rapidly but the communicable diseases are still ahead (Figure II.1)

Figure II.1 Projected deaths by major cause and World Bank income group, all ages, 2005

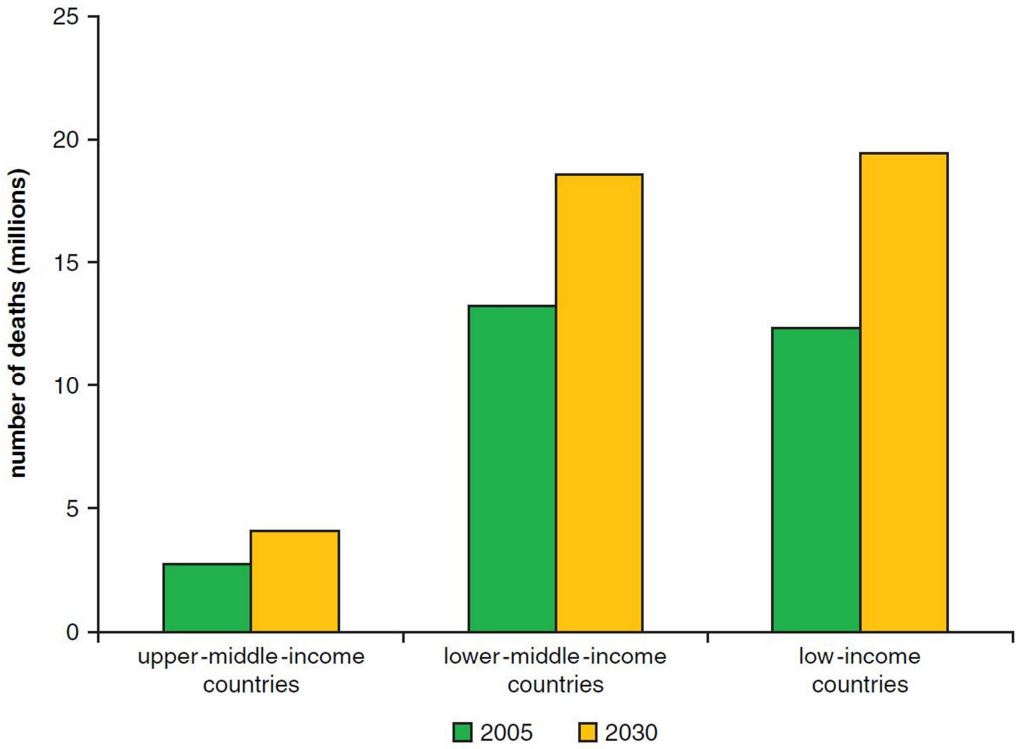


Source: World Health Organization (2005) Preventing chronic diseases: a vital investment : WHO global report.

Chronic diseases such as cardiovascular disease (CVD), diabetes, obesity, cancer and respiratory diseases cause more than half of the 58 million deaths that occur each year worldwide and these are by no means confined to wealthy countries; instead, a large part of this burden falls on low- and middle-income countries. For example, two-thirds of the 177 million people with diabetes live in the developing world. Importantly, one quarter of chronic disease occurs in people younger than 60 years. The resulting long-term morbidity and premature death often pushes affected individuals and their families into poverty or keeps them there through loss of work opportunities and health care costs (WHO, 2006).

The WHO has projected important increases in deaths and illness due to chronic diseases in low- and middle-income countries up to 2030 (Figure II.2).

Figure II.2 Deaths attributed to Chronic Non-communicable Diseases by Word Bank Income Group, 2005



Modified from: Adeyi, O. Smith, O and Robles, S (2007) Public Policy and the Challenge of Chronic Noncommunicable Diseases. World Bank. Washington, DC

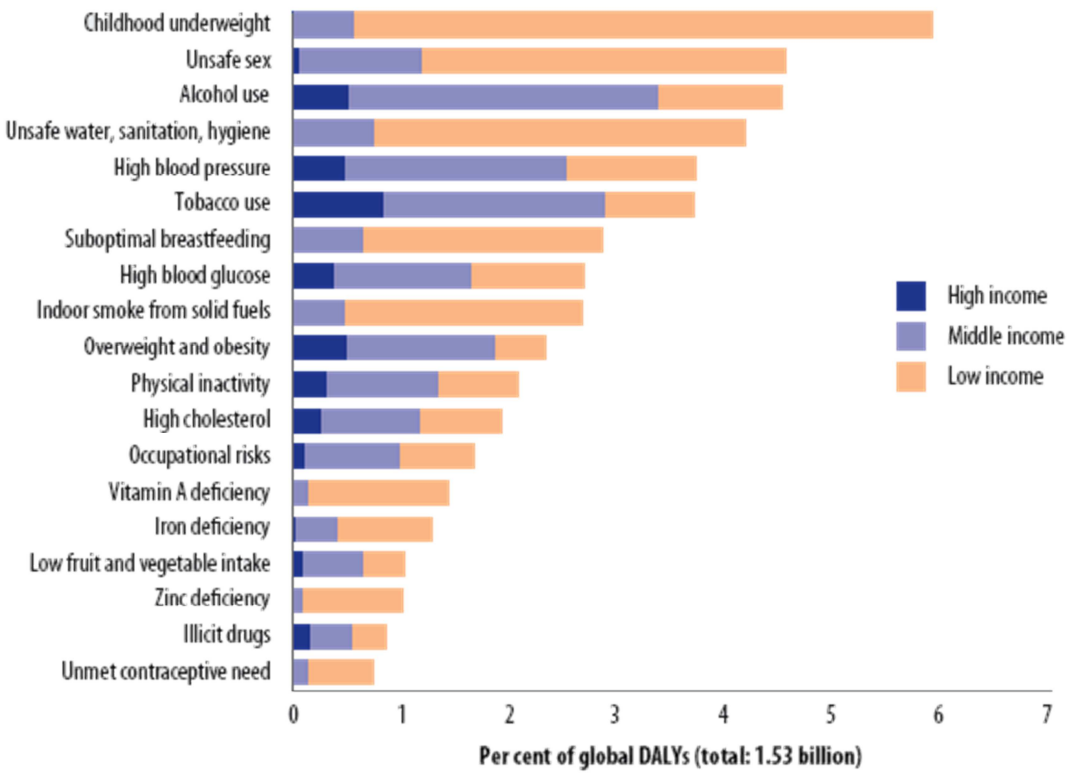
Latin American and Caribbean people spend a large portion of their lives in a state of poor health. The average people lives around 10 years of his or her life in bad health and, as various studies have shown, women are the hardest hit because of their higher morbidity rate and the cumulative effect of a lifetime of inequality (Anderson and Chu, 2007).

Chronic non-communicable diseases are the main cause of disability and death worldwide. This reflects new risks factors (e.g., obesity) that tend to show a greater contribution

compared to more traditional risk factors for low and middle income countries (e.g., inadequate nutrition, unsafe water and sanitation (WHO, 2006) Figures II.3 and II.4

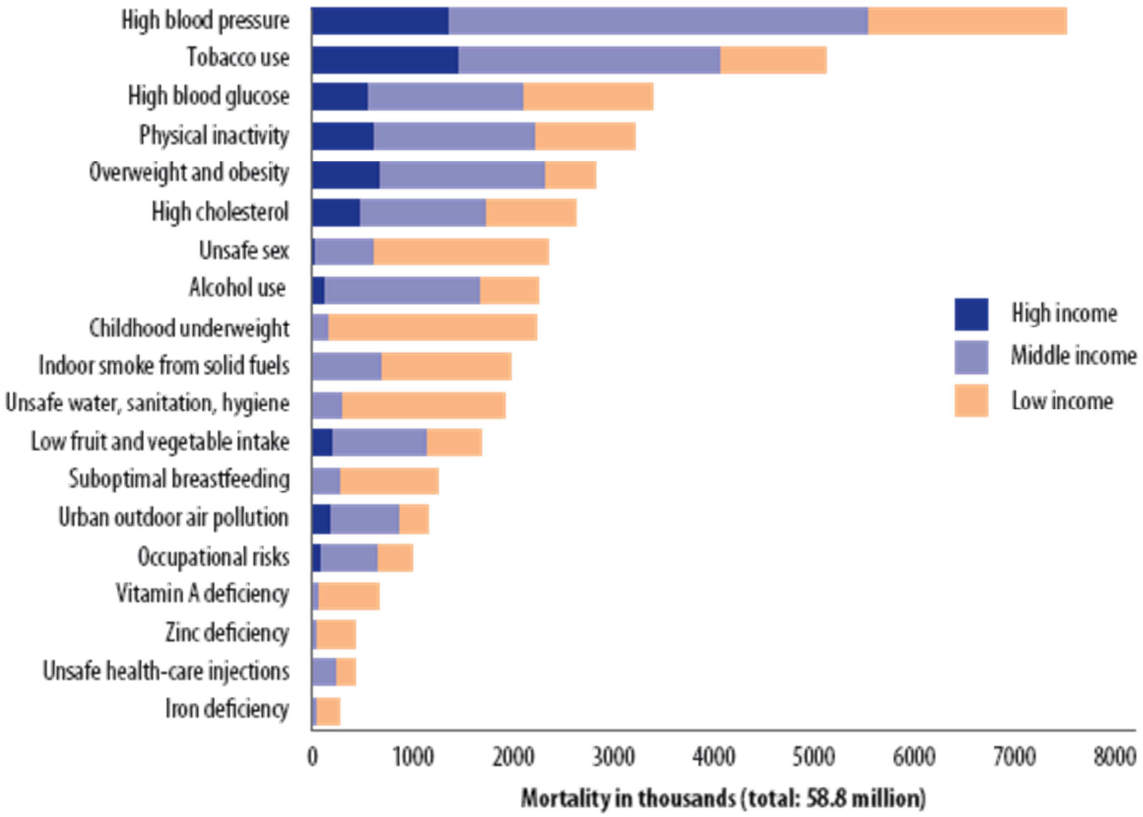
Therefore, overall, lower-income countries suffer heavier disease burden. An analysis of lost years of health also shows that communicable diseases are much more of a burden for the poorest countries than for medium- to high-income countries. This pattern is repeated within countries themselves, where those on lowest incomes are subject to higher risks of communicable diseases (WHO, 2006).

Figure II.3 Percentage of disability-adjusted life years (DALYs) attributed to 19 leading risk factors, by country income level, 2004



Source: WHO (2006). Global Burden of Disease and Risk Factors. New York: World Health Organization

Figure II. 4 Deaths attributed to 19 leading risk factors, by country income level, 2004



Source: WHO (2006). Global Burden of Disease and Risk Factors. New York: World Health Organization

These epidemiological transitions in population health currently being experienced in low- and middle-income countries are compressed into a shorter time frame than that experienced historically in high-income countries.

Much of the chronic disease burden in low and middle-income country settings can be attributed to environmental and lifestyle factors, including tobacco consumption and decreased physical activity. Variations in the risk of non-communicable diseases between high income countries and trends over time within countries also suggest that the factors

determining incidence are modifiable, and therefore that many non-communicable diseases are preventable (WHO, 2002, WHO, 2006). Despite this wealth of information, there is an important research gap between developing and developed countries.

Research findings from developed settings are not necessarily appropriate to other contexts; thus, local knowledge is imperative (Miranda et al., 2008). For example, higher body mass index is more likely to be associated with lower socio-economic status and worse general health (e.g. cardiovascular risk) in a developed nation setting but with higher socio-economic status and better health (e.g. improved nutrition) in a lower income setting.

II.3 Conclusions

As more people live until advanced old age, these demographic changes imply much more than just than aging and an increase in chronic morbidity.

The epidemiological transition in high and LMIC, has important differences and needs. But they have in common, the increase of age-associated conditions, chronic diseases, disability and dependence. Among these age associate conditions, dementia is an important cause of disability and death.

Chronic non-communicable diseases are the main cause of disability and death worldwide; and they represent a high socio-economical cost all over the world.

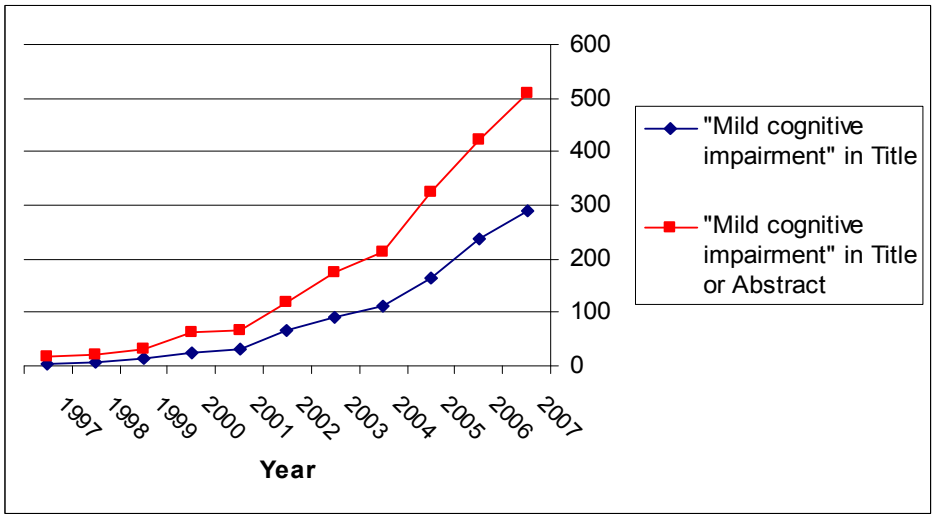
III. - MILD COGNITIVE IMPAIRMENT - ASCERTAINMENT AND DEFINITION OF TERMS

III.1 The importance of mild cognitive impairment concept

Having considered the importance of demographic ageing and the shift from communicable to non-communicable diseases in many low and middle-income countries, the aim of this chapter is to review mild cognitive impairment (MCI) as a construct of particular interest to rapidly ageing populations, with particular attention paid to the development of the concept and diagnostic criteria, issues which need to be considered when interpreting its epidemiology and correlates.

If interventions are to be developed to reduce the impact of dementia, then waiting until the clinical manifestations become apparent is likely to be too late, given the long prodromal period for most causes of the disorder. Research into cognitive aging and dementia is therefore focusing increasingly on the characterization of the earliest stages of cognitive impairment (Petersen et al., 2001), and a variety of clinically defined pre-dementia syndromes with differing diagnostic criteria and nomenclature have been proposed to describe non-disabling but symptomatic cognitive deficits arising in older people (Panza et al., 2005). In this century, attention has focused on MCI as a term with growing usage in the international scientific literature on cognitive aging and dementia (Petersen, 2004). This fact is evidenced by an exponential increased in publishing articles utilizing this term (Figure III.1). In spite of the fact that MCI remains a controversial entity in terms of its precise definition and reliability, it is largely accepted as a ‘concept’ describing a situation where a person is more cognitively impaired than would be expected for their age/background and yet does not fulfil criteria for dementia.

Figure III.1 PUBMED search "mild cognitive impairment" (1997-2007)



The difficulty in standardising case definitions for MCI over the last 10 years, has led to several international consensus meetings, and publication of proposed criteria; for example, the meeting on "Current Concepts in Mild Cognitive Impairment" held in 1999 in Chicago (Petersen et al., 2001), the Annual Mild Cognitive Impairment Symposium (Bain, 2006), the first symposium of the International Working Group on Mild Cognitive Impairment in Sweden(Winblad et al., 2004), or the 2006 International Psychogeriatric Association Expert Conference on Mild Cognitive Impairment (Gauthier et al., 2006).

The MCI concept has tended to become more, rather than less, complex over time, leading to considerable debate over practice guidelines and competing sets of criteria (Ganguli and Petersen, 2008). To date, no single construct is universally accepted for defining MCI, and this has given rise to inconsistencies within and between clinical and research settings with heterogeneous populations and differences in aetiological factors, cognitive changes and clinical outcomes (Matthews et al., 2007, Panza et al., 2005). There is therefore a need to have clear descriptive and operational definitions of MCI (Collie et al., 2002, Hogan and

McKeith, 2001) and at the same time, to develop studies using different samples and designs in order to achieve a more comprehensive picture of the phenomenon under investigation (Tuokko and Hultsch, 2006). However, important practical questions relating to the concept of MCI need to be addressed, such as its utility, limitations, implications and applicability.

MCI as a construct will inevitably include both 'normal' and 'abnormal' trajectories of decline, the former encompassing a range of cognitive changes that accompany normal aging which do not progress to dementia, although which might place an individual at increased risk of this (Stephan et al., 2007). Factors potentially affecting so-called cognitive aging include education, intelligence, and sensory abilities (Drag and Bieliauskas, 2010) and, given these and the many other potential extraneous influences on the cognitive aging process, is not surprising that inter-individual variability increases with age (Ardila, 2007). It is recognised that some cognitive changes occur as a 'normal' consequence of aging. 'Cognitive aging' is characterized by a decrease in the efficiency of some mental functions; these changes are varied, but they usually do not impact overall functionality. In general the main cognitive changes associated with age are related to information processing speed, executive function and memory (Finkel and Pedersen, 2000, Salthouse, 1996). It is clear that memory decline occurs in aging people; however, while changes in memory can be a normal part of aging, some forms of memory changes may indicate an underlying dementia (Zaudig, 2002, Smith and Rush, 2006). Usually prospective and working memory are most affected with semantic and procedural memory the most stable modalities (Backman, 2008, Grady and Craik, 2000).

Cognitive function at a given age is a product of the level attained by early adult life, commonly referred to as 'cognitive reserve', as well as by intervening changes, whether pathological or 'normal'. Indices of cognitive reserve are positively associated with cognitive performance in multiple domains including attention and memory (Corral et al., 2006) and, as well as influencing the level of function from which age-related decline occurs, may also be a protective factor against the expression of age-related cognitive decline. For example, cognitive reserve has been suggested to moderate the relation between age-related pathology and cognitive functioning (Drag and Bieliauskas, 2010)

III.2 Terminology and concept development for MCI and related constructs

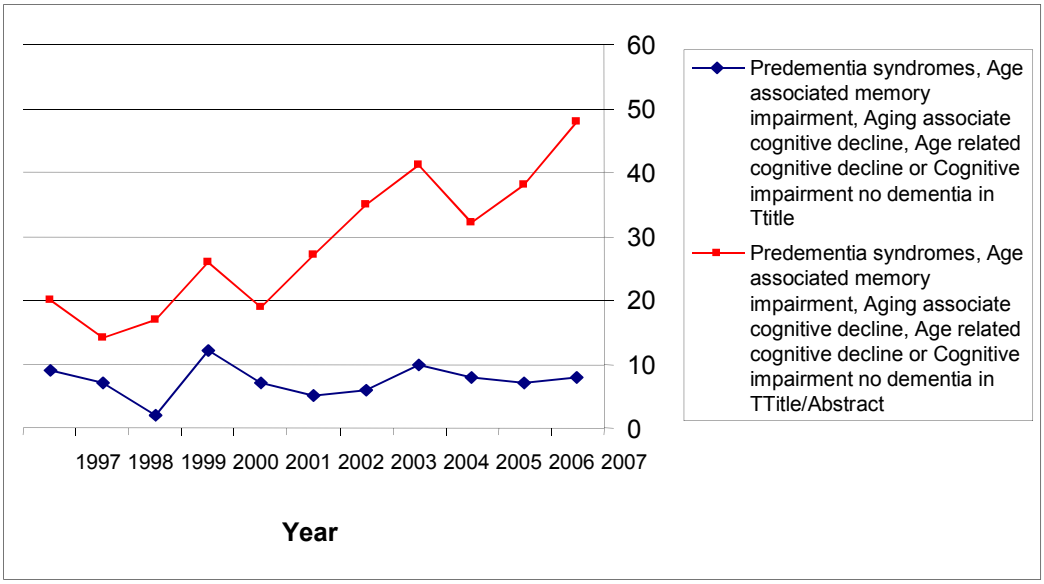
One of the first attempts to identify people with early stages of cognitive impairment (therefore assumed to be at risk of developing dementia) was carried out more than 45 years ago, by Kral (1962) who proposed the terms 'benign' and 'malignant' 'senescent forgetfulness' to describe forms of cognitive decline distinguishable on the basis of symptoms, course and prognosis. Since then, a wide variety of criteria and definitions have been proposed, offering a problematically large number of options:

1. Benign senescent forgetfulness (BSF) (Kral, 1962)
2. Malignant senescent forgetfulness (MSF) (Kral, 1962)
3. Limited cognitive disturbance, (LCD) (Gurland et al., 1982)
4. Age-associated memory impairment (AAMI) (Crook et al., 1986)
5. Late-life forgetfulness (LLF) (Blackford and La Rue, 1989)
6. Mild cognitive impairment (MCI) (Zaudig, 1992)
7. Mild cognitive disorder (MCD) (Christensen et al., 1997)
8. Aging-associate cognitive decline (AACD) (Levy, 1994)

9. Age-related cognitive decline (ARCD) (Levy, 1994)
10. Mild neurodegenerative decline (MND) (Rediess and Caine, 1996)
11. Cognitive impairment no dementia (CIND) (Graham et al., 1997)
12. Mild cognitive impairment (MCI) (Petersen et al., 2001)

A PUBMED search was carried out in order to compare the number of publications using terms different to MCI, the results are summarised in Figure III.2. A comparison between Figures III.1 and III.2 suggests that the MCI term is ten times more often cited than all the others taken together.

Figure III.2 PUBMED search using PDS, AACD, ARCD, and CIND. (1997-2007)



PDS= Pre-Dementia Syndromes, **AACD**= Age-associated cognitive decline, **ARCD**= Age-related cognitive decline, **CIND**= Cognitive impairment no dementia

The MCI term has been applied in different ways. In the 1980s it was used in conjunction with two independent staging systems for progressive aging and dementia associated with Alzheimer's disease: the Clinical Dementia Rating (CDR) scale (Hughes et al., 1982) and

the Global Deterioration Scale (GDS) (Reisberg et al., 1988), where MCI is equivalent to a CDR score of 0.5 ('questionable dementia') and/or a GDS score of 3.

Redies and Caine (1996), in an attempt to summarize and organize the different proposals, identified and described a five cluster spectrum of cognitive function, from optimal cognitive aging through to dementia: 1) successful or optimal cognitive aging; 2) age related cognitive decline or age-associate memory impairment (Crook et al., 1986); 3) age associated cognitive decline (Levy, 1994) and MCI (Zaudig, 1992, Smith et al., 1996) 4) questionable dementia and mild neurocognitive disorder (Rediess and Caine, 1996); and 5) dementia (ranging from mild to severe). This proposal represents a very complete spectrum integrated for five different levels of cognitive functioning in older people. Further details of this system are provided in Table III.1

III.3 Actual MCI diagnostic criteria and classification.

In 2001, Petersen proposed a practice parameter, providing a landmark in the "rediscovery" of the entity, as well as the popularization of the terminology (Reisberg and Gauthier, 2008), that was defined by the following criteria: (1) memory complaint preferably corroborated by an informant; (2) objective memory impairment; (3) normal general cognitive function, (4) intact activities of daily living, (5) no dementia.

Currently, attempts are being made to broaden the definition of mild cognitive impairment to include non-memory deficits and impairment in several cognitive domains.

Petersen *et al.* later developed the original MCI (amnestic MCI) into a broader concept of MCI. Amnestic MCI (aMCI) is an individual with memory impairment, and there may be pure (single domain affected) or aMCI multiple-domain, when in the showing deficits thera are othe cognitive functions alterations (for example: language, attention, executive function, and spatial recognition). In this way, the MCI can be subdivided into subtypes, multiple-domain MCI with and without amnesia, and single non-memory domain MCI. These subclassifications of MCI (Fig.III.3) may correspond to the prestage of Alzheimer's disease, Lewy body disease, frontotemporal dementia or vascular dementia (Petersen et al., 2001)

Figure III.3 MCI Clinical classification

Amnestic mild cognitive impairment	**Single domain**
	Multiple domain
Non-amnestic mild cognitive impairment	**Single domain**
	Multiple domain

In conclusion, previous criteria for mild cognitive impairment were specific to isolated deficits in memory; however, developments have extended them so that the definition of mild cognitive impairment now includes a broad range of cognitive deficits and clinical subtypes with many potential causes. In the past, mild cognitive impairment and 'cognitive impairment no dementia' (CIND) could be distinguished by the fact that mild cognitive impairment referred to isolated memory deficits—now called amnestic mild cognitive

impairment (aMCI)—whereas CIND included global cognitive impairment and deficits in several cognitive domains (Gauthier et al., 2006).

Clinical criteria for a-MCI as proposed by the Mayo Clinic group include (Petersen et al., 1999).

1) memory complaint, preferably corroborated by an informant
2) abnormal scores on memory tests relative to age and education matched healthy people
3) normal general mental status,
4) normal daily functioning
5) absence of dementia

In 2004 a report was published by the International Working Group on MCI, where specific recommendations for general MCI criteria were presented: i) the person is neither normal nor demented; ii) there is evidence of cognitive deterioration shown by either objectively measured decline over time and/or subjective and/or informant report of decline in conjunction with objective cognitive deficits; and iii) activities of daily living are preserved and complex instrumental functions are either intact or minimally impaired (Winblad et al., 2004).

Another attempt to integrate the different terms and definitions relating to MCI arose from a systematic review of the literature carried out by Matthews et al (Matthews et al., 2007), where they identified eighteen definitions of early cognitive impairment and mapped them in a complex flow diagram, reproduced in Figure III. 4

A clinical definition of MCI has served investigators for more than 15 years. Recent proposed alternative definitions of the entity have moved increasingly closer to its original clinical definition. Given the volume of research into biomarkers for dementia risk, future definitions may well incorporate biological findings (Reisberg and Gauthier, 2008). MCI therefore remains a term in evolution and, while it still seeks precise and reliable nosological definition, the term continues to reflect an important clinical entity (Burns and Zaudig, 2002).

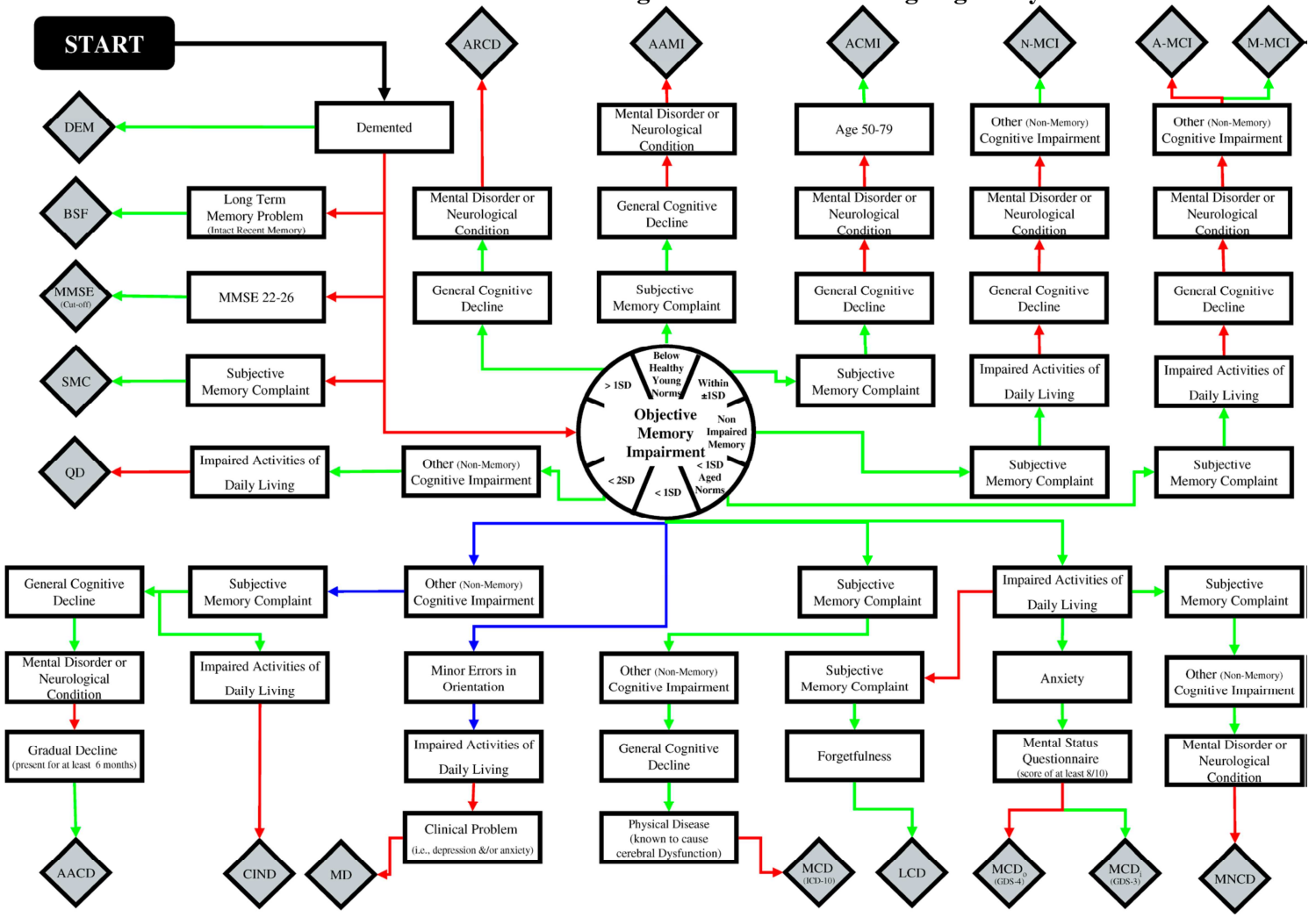
Table III.1 Spectrum of Cognitive Functioning in Later Life

Spectrum levels	***1.Successful cognitive aging***	***2. ARCD or AAMI***	***3. MCI***	***4. MND***	***5. Mild to severe dementia***
Authors		Crook et al. (1986)	Levy (1994) and Zaudig (1992)	Rediess and Caine, (1996)	DSM-IV (APA, 2000) ICD-10 (WHO, 1992)
Description	Minimal cognitive changes	Normal age related cognitive changes	Below average for age peers without functional impairment	Below average for age peers with functional impairment; deficit in at least two cognitive domains	Deficient memory and at least one other cognitive domain affected; with functional impairment
Psychometric features	Above average compared to age peers; within the normal range for younger adults	Above or within the average range for age, but below for younger adults on selected tests	Memory or other cognitive function 1-1.5 *SD* below age peers; impaired retention	Performance on test of at least two cognitive areas 1.-1.5 *SD* below age peers	Performance on memory test and 1 other cognitive area1-2 *SD* below age peers
Functional status	Active, independent, working, or have active retirement	Active, independent, may work or have active retirement	Independent	Need some help in daily activities or has discontinued some normal daily activities.	Clearly impaired social and occupational functioning
Potential contributing factors	High baseline IQ; high education, active retirement	Wider range of baseline IQ with decline referenced to estimated baseline level; good health	Wider range of baseline IQ with decline referenced to estimated baseline level; presence of AD risk factors	Wider range of base line IQ with decline referenced to baseline level; presence of AD risk factors; may include prodromes for atypical dementia syndromes	Appearance of clinically significant features of dementia may be influenced by premorbid level of functioning.
GDS Equivalences	1	1	2	3	> 3

GDS Global Deterioration Scale

Source: Modified from Rediess and Caine (1996).

Figure III.4 Schematic Overview of the Approach Used to Classify MCI across Different Definitions in the Medical Research Council Cognitive Function and Ageing Study



DEM= Dementia, **BSF=** Benign Senescent Forgetfulness, **MMSE=** Mini-mental State Examination, **SMC=** Subjective Memory Complaints, **QD=** Questionable Dementia, **ARCD=** Age-Related Cognitive Decline, **AAMI=** Age associated Memory Impairment, **ACMI=** Amnestic Mild Cognitive Impairment **N-MCI=**Non-Amnestic Mild Cognitive Impairment, **M-MCI=** Multiple Mild Cognitive Impairment, **MD=** Mental Disorders, **AACD=** Age-Associated Cognitive Decline, **CIND=**Cognitive Impairment No Dementia, **MCD=** Mild Cognitive Disorder (International Classification of Diseases 10th Revision),**LCD=** Limited Cognitive Disturbance, **MCD=** Mild Cognitive Decline (Global Deterioration Scale Stage 3); **MNCD=**Mental Disorders Or Neurological Condition

Source from: Matthews et al. (2007). Operationalization of mild cognitive impairment: a graphical approach. PLoS Med, 4, 1615-9

III.4 MCI progression to dementia

Many longitudinal studies have found an increased risk of developing dementia in people defined with MCI (Morris et al., 2001, Panza et al., 2005, Bennett et al., 2002, Petersen, 2004); however, precise diagnostic criteria and delineation of the distinction with dementia have been more elusive. Mild Cognitive Impairment has been associated with an increased risk of developing dementia at a rate of 10 to 15% per year, while the rate of healthy controls is only 1 to 2% per year. In clinical samples, annual progression from MCI to dementia ranges from 12 to 17%, whereas substantially lower progression rates have been observed in community-based studies (4 to 15% per year) (Manly et al., 2008).

III.5 Conclusions

MCI is a construct of particular interest now that the world is having a marked increase in the older population, and mainly for those rapidly ageing populations.

MCI concept has been showing an important development along the time, previous criteria for mild cognitive impairment were very focus on memory deficits; however, they have been extended and now include a broad range of cognitive deficits and clinical subtypes associated to potential aetiologies.

MCI represents the hope of earlier case identification and as consequence, more effective treatment interventions.

IV.-MILD COGNITIVE IMPAIRMENT EPIDEMIOLOGY, COMMUNITY STUDIES

IV.1 Importance of definition and methodology

As has been described, the concept of Mild Cognitive Impairment (MCI) has undergone a number of changes and remains ambiguously defined, so that the prevalence of this entity may vary substantially between studies according to the definition applied, as the methodology, setting and sample size (Busse et al., 2003a).

IV.2 Community prevalence studies

A systematic review of community prevalence studies of MCI within the last 10 years was carried out first for MCI as a broad construct, studies were only selected as relevant if they had sample sizes of at least 1000 and findings are summarized in Table IV.1. As described earlier, the methodology of MCI studies is recognised to be potentially highly important and this was considered in the review. Measurements of cognitive function used to derive case operational definitions have varied substantially, clearly illustrated in the instruments column of Table IV.1 where we can see for example, in Frisioni *et al.* (2000) study, that only the Mini-Mental State Examination (MMSE) was used, but with several different approaches in terms of calculating cut-offs (for example, varying in the use of age and education standardization), contrasting with Manly´s (2005, 2008), Gavrila (2009) and Petersen´s (2001, 2010) studies where more than five instruments were used.

Community studies with 1000 and more subjects chosen for this review has reported a wide range of prevalence (from 2 to 31%), this variability being associated substantially with the definition criteria of MCI used.

A more focused systematic review of community prevalence studies of aMCI within the last 10 years was carried out next (Table IV.2), but in this case without the selection

criterion related to sample size, because the number of community studies for this particular subtype is small. When aMCI was defined according to Petersen's revised criteria (Petersen et al., 2001), the observed prevalence ranged from 2.1% (Palmer et al., 2008) to 11.5% (Petersen et al., 2010) and was most commonly found to be around 3-5% (Busse et al., 2003a, Ritchie et al., 2001) with a few exceptions in older samples (Dickerson et al., 2007, Rapp et al., 2010, Yaffe et al., 2011, Petersen et al., 2010).

Reports of the community prevalence of aMCI have been predominantly derived from European and North American populations. Estimates of aMCI prevalence were 6% in Kolkata, India (Das et al., 2007), and 4.5% for Chongqing, China (Li et al., 2011). Higher prevalences have reported for Malaysia (15.4%) (Lee et al., 2011) and for South Korea (9.7%) (Kim et al., 2011).

.

Table IV.I Large (n>1000) community prevalence studies of MCI

Study	Sample size	Age range	Setting	Methodology	Prevalence (%)	Instrument	Overall study objective
Frisoni (2000)	1435	75-95	Sweden	Cross sectional	15.9	MMSE	Relationship between physical health and MCI
Kivipelto (2001)	1449	65-79	Finland	Cross sectional	6.1	MCADRC	Prevalence of MCI in elderly
Larrieu (2002)	3777	65	France	Cohort	2.8 to 3.5	MMSE, BVRT, Katz, ADLS	Estimate age-specific incidence rate of MCI according to sex and educational level
Busse et al.(2003a)	1045	>75	Germany	Cohort	3.1	SIDAM	Age-specific prevalence, incidence and predictive validities for MCI concepts
Fisk, (2003)	1790	>65	Canada	Cross sectional	2 to 3	MMSE	Prevalence estimates and 5 year outcomes of various case definitions of MCI
Busse et al (2003b)	1045	>75	Germany	Cross sectional	3.1 (Modified MCI 5.1)	SIDAM	Age-specific prevalence, incidence and predictive validities for MCI concepts
Lopez (2003)	2470		USA	Cohort	19	Neuropsychological testing CHS	Prevalence of (MCI) and its diagnostic classification
Meguro, (2004)	1501	>65	Japan	Cohort	4.9	MMSE, CASI, GDS, Daily, functioning, CDR	Prevalence and neuropsychological features of MCI
Manly, (2005)	1315	>65	USA	Cohort	5	DFLS, BFAS, SRT, MMSE, BVRT, WAISR, MDRS	Operationalized diagnostic criteria for MCI and prevalence in ethnically and linguistically diverse elders
Busse, (2006)	1045	>75	Germany	Cohort	19	SIDAM,SIDDA MMSE	Time dependent evolution from MCI to dementia
Ekman, (2007)	1800	45-84	Sweden	Cross sectional	31	CDR, TTO	Community-based health utilisation
Manly, (2008)	2364	>75	USA	Cohort	5.1	DFLS, BFAS, MMS, SRT, BVRT, WAISR, MDRS, BNT, CWA, BDAE, RDT	Frequency and course of MCI in a multi-ethnic community
Anstey, (2008)	2222	60-64	Australia	Cohort	4.2	CDR, BDAE, CERAD, RAVLT, MMSE	Estimate incidence rates of MCI and related disorders, and conversion to dementia
Gavrila, (2009)	1074	65-95	Spain	Cross sectional	8.7	MMSE, CAMDEX, HIS BFAS, HDRS, RGDS,	Prevalence of dementia and MCI in general elderly population and associated socio-demographic factors
Petersen (2010)	1969	70-80	Olmsted	Cohort	16	DRS, FAQ, STMS, WAISR, TMT, BNT	Prevalence of MCI

MCI = Mild Cognitive Impairment, **MMSE**= Mini-Mental State Examination, **MCADRC**= MCI criteria suggested by Mayo Clinic Alzheimer´s Disease Research Center, **BVRT**= Benton´s Visual Retention Test, **SIDAM**= neuropsychological test battery (MMSE, clinical judgment, psychosocial impairment), **DRS**= Dementia Rating Scale, **GDS**= Geriatric Depression Scale, **CASI**= Scale wish contains nine domains (long-term memory, short-term memory, attention, concentration/mental manipulation, orientation, visual construction, abstraction and judgment, list-generating fluency, **DFLS**= Disability and Functional Limitations Scale, **BFAS**= Blessed Functional Activities Scale, **SRT**= Selective Reminding Test, **BVRT**= Benton Visual Retention Test, **WAIS**= Wechsler Adult Intelligence Scale , **WAISR**= Wechsler Adult Intelligence Scale Revised, **MDRS**= Mattis Dementia Rating Scale, **BN**T= Boston Naming Test, **CWA**= Controlled Word Association, **BDAE**= Boston Diagnostic Aphasia Examination **RDT**= Rosen Drawing Test, **SIDDA**= Structured Interview for Diagnosis for Dementia Alzheimer-type, **TTO**= Time Trade-off method, **CERAD**= Consortium to Establish a Registry for Alzheimer´s Disease, **TMT**= Trail Making Test , **VSF**= Verbal and Semantic Fluidity, **ROF**= Rey- Osterrieth Figure, **WCST**= Wisconsin Card Sorting Test, **GDSAPDD**= Global Deterioration Scale For Assessment of Primary Degenerative Dementia, **IADLS**= Instrumental Activities Daily Living Scale (Lawton and Brody), **BADLI**= Barthel Activities Daily Living Activities Index, **CAMDEX**= Cambridge Mental Disorders of the Elderly Examination, **HDRS**= Hamilton Depression Rating Scale, **RGDS**= Reisberg Global Deterioration Scale, **HIS**= Hachinski Ischemic Scale, **FAQ**= Functional Activities Questionnaire, **STMS**= Short Test of Mental Status, **PHQ**= self-administered Patient Health Questionnaire from the Primary Care Evaluation of Mental Disorders (PRIMEMD), **RAVLT**=Rey Auditory Verbal Learning Test, **CHSNP**= Cardiovascular Health Study Neuropsychological Testing (Modified Mini-Mental State Examination, the Digit Symbol Test, Benton Visual Retention Test Informant Questionnaire for Cognitive Decline in the Elderly and Dementia Questionnaire modified version of the Center for Epidemiologic Studies–Depression Scale), **PFAQ**= Pfeffer Functional Activities Questionnaire.

Table IV.2 aMCI prevalence community studies

Study	Country	Sample Size	Age Range	aMCI Prevalence
(Hanninen, 1996)	Finland	592	68-78	26.6% AACD
(Graham et al., 1997)	Canada	2914	65 +	16.8%
(Di Carlo et al., 2000)	Italy	3425	65-85	10.7% PCIND 7.5% ARCD
(Ritchie et al., 2001)	France	833	60+	3.2%
(Hanninen et al., 2002)	Finland	806	60-76	5.3%
(Busse et al., 2003a)	Germany	1045	65+	3.1%
(Palmer et al., 2003)	Sweden	1435	75-95	18% future dementia cases
(Lopez et al., 2003)	USA	927	75+	6%
(Ganguli et al., 2004)	USA	1248	65+	4%
(Meguro et al., 2004)	Japan	1501	65+	4.9%
(Jungwirth et al., 2005)	Austria	302	75	0.5%
(Manly et al., 2005)	USA	1315	65+	5.0%
(Das et al., 2007)	India	960	50+	6.04%
(Di Carlo et al., 2007)	Italy	2768	65-84	7.0%
(Dickerson et al., 2007) (retrospective)	USA	244	65+	11.1%
(Manly et al., 2008)	USA	2364	65+	21.8%
(Palmer et al., 2008)	Sweden	1379	75-95	2.1%
(Ravaglia et al., 2008)	Italy	1016	65+	4.1%
(Gamaldo et al., 2010)	USA	554	50-95	4%
(Boyle et al., 2010)	USA	761	70+	40%
(Dlugaj et al., 2010)	Germany	4145	50-80	3.5%
(Ganguli et al., 2010)	USA	2036	65+	2.27%
(Kochan et al., 2010)	Australia	987	70-90	4.6%
(Petersen et al., 2010)	USA	1969	70-89	11.5%
(Rapp et al., 2010)	USA	447	65+ women	6.3%
(Kim et al., 2011)	Korean	1673	65+	9.7%
(Lee et al., 2011)	India	318	60+	15.4%
(Yaffe et al., 2011)	USA	1299	≥85 women	aMCI = 7.9 (13.0% if aMCI single + multiple domain)

aMCI= amnesic Mild Cognitive Impairment

IV.3 MCI Associations with demographic status

Demographic associations of principal interest have been age, gender and education, as summarized in Table IV.3. Female gender, increased age, lower education and lower socio-economic status are associated with dementia (Fratiglioni et al., 2010) and have also been described in association with MCI (Manly et al., 2005).

IV.3.1 Age

A consistent relationship between increased age and MCI has been found reasonably consistently, in 13 of the 17 studies in Table IV.3 with only one study reporting no association and three not reporting analyses of this.

IV.3.2 Gender

Of the 17 studies in table IV.3 five reported a positive association mainly with male gender more strongly associated with the development of MCI (Anstey et al., 2008, Gavrila et al., 2009, Lopez et al., 2003, Petersen et al., 2010), and only one with female gender (Fisk et al., 2003) while eight did not report this and four no association (Frisoni et al., 2000, Larrieu et al., 2002, Busse et al., 2006, Ekman et al., 2007, Busse et al., 2003a).

IV.3.3 Education

Eight of the 17 studies found a positive association between higher education and lower prevalence of MCI, with only two studies (Fisk et al., 2003, Frisoni et al., 2000) finding no association.

Table IV.3 Main associations with MCI prevalence

Study	Sample size	Age range	Setting	Prevalence %	Associations with demographic status		
					Age	Gender	Education
Frisoni, (2000)	1435	75-95	Sweden	15.9	Negative	NR	NS
Kivipelto, (2001)	1449	65-79	Finland	6.1	Positive	NR	High educational level
Larrieu, (2002)	3777	65	France	2.8(3.5)	Positive	NR	High educational level
Busse, 2003	1045	>75	Germany	3.10	Positive	NR	NR
Fisk, (2003)	1790	>65	Canada	3.02	Positive	Female	NS
Busse, 2003	1045	>75	Germany	1 -15*	Positive	NS	NR
Lopez, 2003	2470		USA	19	Positive	Men	NR
Ganguli, (2004)	1248	>65	USA	3 to 4	NR	NR	NR
Meguro, (2004)	1501	>65	Japan	4.9	Positive	NR	Less years of education
Manly, (2005)	1315	>65	USA	5	Positive	NR	Less than 9 years of education
Busse, (2006)	1045	>75	Germany	19 -42*	Positive	NS	NR
Ekman, (2007)	1800	45-84	Sweden	31	Positive	NS	NR
Arboleda, (2008)	1040	>65	Colombia	9.7	NR	NR	NR
Manly, (2008)	2364	>75	USA	5.1	Positive	NS	Less than 12 years of education
Anstey, (2008)	2222	60-64	Australia	4.2	NR	Men	Less years of education
Gavrila, (2009)	1074	65-95	Spain	8.7	Positive	Men	Less years of education
Petersen, (2010)	1969	70-80	Olmsted	16	Positive	Men	Less years of education

*depending on subset employed

MCI= Mild Cognitive Impairment, **NR=** Not Reported, **NS=** No significant association, **USA=** United States of America

IV.4 Associations with neuropsychiatric symptoms/status

Recent studies suggested that MCI is associated with neuropsychiatric symptoms (Feldman et al, 2004; Liketsos et al, 2002; Cummings, et al, 2003), cited as being of potential importance for defining sub-groups at higher risk of developing dementia in the future. Two studies have reported associations between depression and MCI prevalence (Frisoni et al., 2000, Kivipelto et al., 2001) although with limited information on syndrome definition.

IV.5 Other associations

Poor physical health has been implicated in relation to early stages of cognitive deterioration, although associations with cognitive disturbance may have other pathways besides dementia (Frisoni et al., 2000). Higher mortality rates have been reported to be associated with MCI, supporting the association with worse health.

IV.6 Conclusions

Epidemiological studies of MCI and aMCI have shown considerable heterogeneity in output, at least some of which has arisen because of methodological sources of variability such as in case definition, instruments used for evaluating cognitive functioning, populations studied and methods used to analyse and present results (Fisk et al., 2003, Golomb et al., 2004, Panza et al., 2005, Busse et al., 2003a). MCI and aMCI have been challenging constructs to apply in population-based studies because of ambiguities in the clinical criteria, which are difficult to operationalize (Panza et al., 2005, Ritchie et al., 2001).

V. - SUBJECTIVE MEMORY COMPLAINTS

V.1 Introduction, concept and definitions

Before reviewing empirical data, it is important to consider the terminology, concept and definitions, which are many and varied. In essence, the conceptual basis behind these approaches is related to the concerns of a person's view of their memory or another aspect of cognitive function, in particular, identifying instances where people feel that their cognitive function is poor or has declined and report this – either spontaneously or to direct questioning. Terminology describing this in research studies has been variable, including the following phrases:

-subjective memory and/or cognitive complaints

-subjective memory and/or cognitive impairment

-subjective memory and/or cognitive problems

-subjective memory and/or cognitive deficits

For this chapter the term "subjective memory complaint" will be used because it was the most prevalent term found in this review and it describes best the relevant criterion for MCI. Almost without exception instruments applied in surveys of older people ask about memory rather than other cognitive functions and they tend to focus on perceived memory deficits which are problematic or noticeable – i.e. better expressed as 'complaint' rather than 'impairment', although community studies have tended to screen for the complaint through direct questioning rather than investigate spontaneous reporting of this or self-initiated clinical presentations.

Variability in the definitions of subjective memory complaint (SMC) (also frequently termed subjective memory impairment (SMI) was highlighted in the review by Abdulrab

and Heun (2008) where, of 515 citations identified, only 44 contained definitions. Specifically, it was concluded that there was a lack of consistency in how SMC was defined and the authors proposed a set of criteria aimed to increase specificity of memory complaints and recommended international consensus on such criteria by experts in the field.

In the literature reviewed for this chapter, various types of questions have been employed to determine the presence of SMC:

- Use of a single question on deficient memory/cognition with a yes/no response (SMC categorized by yes or no response)
- Use of a single question on deficient memory/cognition with a scaled/graded response (SMC categorized by certain responses)
- Use of scales composed of a set of question with yes/no responses. A person must answer a minimum number of questions in the affirmative to be categorized with SMC
- Use of a questionnaire or subscale composed of questions with scored responses. The overall score must be over a threshold to indicate SMC (SMC categorized by cut-off score)

Abdulrab and Heun (2008) recommended for future studies in SMC that it might be helpful to include a comprehensive set of criteria to help identify people with memory complaints who are at a higher risk of memory decline and future dementia. These criteria could be used as a guide for further research to determine what aspects of memory complaints are most relevant in predicting future cognitive decline. These are displayed here for

illustrative purposes; however, they run the risk of creating yet another 'MCI equivalent' and lack empirical data to support their application at present.

Proposed essential criteria include:

- Age at presentation, for example over the age of 50 years.
- The presence of memory complaints in a specified length of time - for example in the past 6 months.
- The belief that one's memory is worse compared to earlier periods of life - for example when one was in high school or college.
- Provision of a valid example in which memory problems occur in everyday life.
- Frequency of memory problem for example at least every week; and
- Normal objective memory performance (i.e. without dementia).

Cause specific criteria may be taken into account:

- Gradual onset - potentially indicating DAT (dementia of Alzheimer's type).
- Sudden or staggered onset - potentially indicating vascular dementia.

Non-essential but supportive criteria may include:

- The belief that memory is worse than others of similar age.
- Memory worsening affirmed by an informant (close relative or friend who is in contact with subject at least monthly).
- Subject spontaneously mentioning memory problems if asked about any general medical concerns; and
- Seeking medical help for memory problems.

V.2 Community prevalence studies

A review of studies reporting prevalence of SMC or a related construct, was conducted. As in the previous chapter, given the large volume of previous literature and the epidemiological nature of the study to be described, the focus for this literature review was on community studies with a sample size of 1000 or more.

Several international population based studies have estimated the prevalence of subjective memory complaints (SMC). Jonker et al (2000) reviewed studies of the prevalence of memory complaints and the relationship between memory complaints and impairment or decline (or dementia) in older people. In this review, the prevalence reported ranged from 25% to over 50%.

Findings on prevalence for the SMC community studies with 1000 or more participants was from 4.6 to 69%, the most of them fall around Jonker´s reported range and only few of them are much lower, such as those in the study by Geerlings et al (1999) where the prevalence was 10.8% and that that reported by Van Oijen (2007) of 18.9%. Most used a single question and those reporting the highest prevalences tended to involve this approach, suggesting that the nature of the question is important in determining the likelihood of a positive response. Surveys using more than one item or a scale and cut-off have tended to give prevalence's in the range of 10-30% and are most likely ascertaining complaints, which are both, present and felt to be problematic or noticeable (Table VI.1)

Table V.1.Summarizing community studies with sample sizes of at least 1000 reporting SMC prevalence

Lead author, year	Sample size	Inclusion age range	Country	SMC ascertainment	Methodology	Prevalence (%)
Cuttler (1988)	14,783	≥ 55	USA	Single question yes/no (+ frequency)	Cross sectional	15.3
Geerlings (1999)	3,778	65 - 84	Netherlands	Single question (4 categories)	Cross sectional	10.8
Benito L (2010)	2,679	≥ 55	Spain	Single question	Longitudinal	40.0
Gagnon (1994)	2,276	≥ 65	France	Single question	Cross sectional	33.5
Jonker (1996)	2,537	65 – 85	Netherlands	CAMDEX 3 questions (4 categories)	Cross sectional	34.2
Blazer (1997)	4,162	≥ 65	USA	Single question	Longitudinal study	55.5
Montejo (2011)	1,637	>64	Spain	Single question	Cross sectional	32.4
Dik (2001)	1,168	62 – 85	Netherlands	Single question	Longitudinal study	25.5
St John (2002)	1,416	≥65	Canada	Single question	Longitudinal study	21.0
Comijs (2002)	2,032	55 – 85	Netherlands	Single question	Longitudinal study	23.0
Palmer (2003)	1,435	75 – 95	Sweden	Single question	Longitudinal study	32.0
Kim (2003)	1,204	≥ 65	South Korea	Scale and cut off (GMS)	Cross sectional	22.2
Wang (2004)	1,883	≥ 65	USA	Scale and cut-off	Longitudinal study	4.6
Jorm (2004)	2,546	60 – 64	Australia	2 questions	Cross sectional	10.1
Park (2007)	9,477	≥ 65	South Korea	Single question	Cross sectional	57.3
Oijen (2007)	7,983	≥ 55	Netherlands	Single question	Longitudinal study	18.9
Jessen (2007)	2,389	75 – 89	Germany	2 questions (including presence of worry)	Cross sectional	68
Stewart (2008)	1,779	≥ 65	France	Scale cut off (GMS)	Cross sectional	22.2
Jessen (2010)	2,415	≥ 75	Germany	2 questions (including presence of worry)	Longitudinal study	58.4

USA= United States of America, **CAMDEX=** Cambridge Mental Disorders of the Elderly Examination, **GMS=** Geriatric Mental Status Schedule

V. 3 Principal findings on factors associated with SMC

V.3.1 Demographic factors – age, gender and education

Findings from the studies cited above with respect to demographic associations are summarised in Table V.2. Associations between age and SMC prevalence have not been entirely consistent, older age more often was not associated with higher SMC prevalence (Cutler and Grams, 1988, Blazer, 1997, Dik et al., 2001, Comijs et al., 2002, Wang et al., 2004, Park et al., 2007, Stewart et al., 2008) and studies which have reported no association with age have tended to have smaller (<1000) sample sizes (Tobiansky et al., 1995, Riedel-Heller et al., 1999, Wang et al., 2000, Stewart et al., 2001b, Jungwirth et al., 2004, Balash et al., 2010, Trouton et al., 2006, Park et al., 2007, Stewart et al., 2008), although they do include four of the studies cited in Table V.1 above (Gagnon et al., 1994, Kim et al., 2003, Jorm et al., 2004, Jessen et al., 2010).

Similar to older age, SMC prevalence is most often found to be higher in women than men (Cutler and Grams, 1988, Gagnon et al., 1994, Kim et al., 2003, Stewart et al., 2008, Jessen et al., 2010, Park et al., 2007) although Jorm (2004) and Wang (2004) found the opposite association with higher prevalence in men.

Regarding education, most have found SMC prevalence to be higher in groups with lower education (Jonker, 1996, Comijs et al., 2002, Jorm et al., 2004, van Oijen et al., 2007, Jessen et al., 2010) although several studies have found no significant association with education (Kim et al., 2003, Wang et al., 2004, Jessen et al., 2007, Blazer, 1997) and one reported an association with higher education (Geerlings et al., 1999).

Table V.2. Summarizing community studies with sample sizes of at least 1000 reporting associations between SMC and demographic factors (age, gender and education)

Lead author, year	Sample size	Inclusion age range	Country	Significant associations between SMC and demographic variables		
				Age	Gender	Education
Cutler,(1988)	14,783	55 +	USA	Older age	Female	-
Park, (2007)	9,477	≥ 65	Korea	Older age	Female	Lower
Oijen, (2007)	7,983	> 55	Netherlands	Older age	N/A	Lower
Blazer,(1997)	4,162	≥ 65	USA	Older age	N/A	N/A
Geerlings,(1999)	3,778	65 – 84	Netherlands	N/A	N/A	Higher (>8 years)
Jorm,(2004)	2,546	60 – 64	Australia	N/A	Male	Lower
Jonker,(1996)	2,537	65 – 84	Netherlands	-	N/A	Lower IQ
Jessen,(2010)	2,415	>75	Germany	Older age	Male	Lower
Jessen,(2007)	2,389	75 – 89	Germany	N/A	N/A	N/A
Gagnon,(1994)	2,726	≥ 65	France	N/A	Female	N/A
Comijs,(2002)	2,032	55 – 85	Netherlands	Older age	N/A	Lower
Wang, (2004)	1,883	>65	USA	Older age	N/A	Lower
Stewart,(2008)	1,779	>65	France	Older age	Female	Lower
St John,(2002)	1,416	>65	Canada	Older age	Male	Lower
Kim, (2003)	1,204	>65	South Korea	N/A	Female	N/A
Dik, (2001)	1,168	62 – 85	Netherlands	Older age	N/A	N/A

SMC= subjective memory complaints, **USA=** United States of America, **N/A=** Not Available

V.3.2 Depression, social activity and physical health

Reported associations between SMC and depression-related outcomes in larger surveys are summarized in Table V.3 and can be seen to be uniformly positive whether depressive symptoms have been modelled as a continuously distributed scale or a binary 'case' outcome derived from a scale cut-off or diagnostic instrument (e.g. GMS).

SMCs have been reported to be associated to lower social activity in an unadjusted secondary analysis of one large survey (Stewart et al., 2008), but this association has received little other evaluation. Other reported associations with SMC in larger surveys have included poor physical health and decreased physical activity (Jonker et al., 2000, Minett et al., 2008, Mitchell, 2008) (Table V.3).

Table V.3 Associations between SMC and depression

Study/year	Sample size	Age	Country/ city	Depression measure	Depression outcome analysis	Association
Blazer (1997)	4162	65+	USA	CES-D	Continuous	Positive
Geerlings (1999)	3774	65-84	Netherlands	GMS	Binary (prevalence 9.7%)	Positive
Comijs (2002)	3107	55-85	Netherlands	CES-D	Continuous	Positive
Gagnon (1994)	2726	65 +	France	CES-D	Binary (prevalence 13.4%)	Positive
Jorm (2004) (a)	2546	60-64	Australia	GHQ	Continuous	Positive
Jonker (1996)	2537	65-84	Netherlands	GMS	Continuous	Positive
Jessen (2010)	2415	75+	Germany	GDS	Continuous	Positive
Jessen (2007)	2389	75-89	Germany	GDS	Continuous	Positive
Grut, (1993)	2368	75+	Sweden	CPRS	Binary	Positive
Schmand (1997)	2114	65-84	Netherlands	GMS	Continuous	Positive
Wang (2004)	1883	65 +	China	GDS	Continuous	Positive
Stewart (2008)	1779	65+	France	CES-D	Binary (prevalence 13.3%)	Positive
St John (2002)	1416	65+	Canada	CES-D	Binary (prevalence 11.3%)	Positive
Kim (2003)	1204	65+	South Korea	GMS	Binary (prevalence 12.6%)	Positive
Dik (2001)	1168	55-85	Netherlands	CES-D	Binary (prevalence 10.7)	Positive

CES-D= Centre for Epidemiologic Studies Depression Scale , **GMS=** Geriatric Mental State Schedule, **GHQ=** General Health Questionnaire, **GDS=** Geriatric Depression Scale, **CPRS=** Comprehensive Psychopathological Rating Scale

V.3.3 Cognitive impairment

The prevalence of objective memory impairment has been suggested to be approximately half that of SMC (Mitchell, 2008) and the ‘‘accuracy’’ of SMC in terms of associations with objectively measured cognitive function is controversial. In their review paper, Reid and McLlullich (2006) concluded that SMCs were inconsistently related to current cognitive impairment. Focusing on larger community studies only a few report a significant association in unadjusted analyses (Gagnon et al., 1994, Jessen et al., 2007, van Oijen et al., 2007) and others only after adjustments (Jorm et al., 2004, Stewart et al., 2008). Several large studies did not find an association between SMCs and cognitive functioning (Blazer, 1997, Geerlings et al., 1999, Dik et al., 2001, van Oijen et al., 2007, Park et al., 2007, Jessen et al., 2010, Jonker, 1996, Wang et al., 2000) (Table V.4) . Considering those, which did find an association, it is possibly noteworthy that most reported relatively low SMC prevalence (Table V.1) suggesting that the specificity of the question(s) may have some influence over the associations observed. Specifically, it is possible that a broad question asking about any memory deficit may have too high a level of measurement error whereas one which asks about problematic and/or frequent deficits may more readily identify underlying impaired function

Table V.4 – Summarising associations between SMC and cognitive impairment in larger (>1000 participant) community surveys

Lead author, year	Sample size	Inclusion age range (years)	Country	Cognitive function		
				Domain	Test	Result
Park, (2007)	9,477	≥ 65	South Korea	Global	MMSE	N/A
Oijen,(2007)	7,983	> 55	Netherlands	Global	MMSE	+
Blazer,(1997)	4,162	≥ 65	USA	Verbal memory	SPMSQ	N/A
Geerlings,(1999)	3,778	65 – 84	Netherlands	Global	MMSE	N/A
Jorm, (2004)	2,546	60 – 64	Australia	Global	MMSE	+ *
				Verbal Memory Immediate	CVLT	+ *
				Verbal Memory Delayed		+ *
				Psychomotor Speed	Simple/Choice reaction time	+ after adj
				Crystallized Intelligence	Spot the word	+ *
				Executive function	Symbol digit modalities	+ *
				Attention	Digits backwards	N/A
Jonker, (1996)	2,537	65 – 84	Netherlands	Global	MMSE	N/A
				Factual memory		N/A
				Concentration		N/A
				Psychomotor speed		N/A
				Language	Multi source cog battery	N/A
				Verbal memory		+ *
				Verbal abstraction		+ *
				Orientation place		+ *
				Orientation time		N/A
				Verbal fluency		+ *
Jessen, (2010)	2,415	>75	Germany	Global	MMSE	N/A
				Orientation	SIDAM SISCO	N/A
				Language	SIDAM SISCO	N/A
				Perception	SIDAM SISCO	N/A
				Praxis	SIDAM SISCO	N/A
				Reason & problem solving	SIDAM SISCO	N/A
Jessen, (2007)	2,389	75 – 89	Germany	Verbal fluency	CERAD	+
				Verbal memory	SIDAM	+ *
Gagnon, (1994)	2,276	≥ 65	France	Visual memory	BVRT	+
				Verbal memory	WMS	+
Comijs, (2002)	2,032	55 – 85	Netherlands	Global	MMSE	+
Wang, (2004)	1,883	>65	USA	Global	CASI	N/A
Stewart, (2008)	1,779	>65	France	Global	MMSE	+ *
St John, (2002)	1,416	>65	Canada	Global	MMSE	+
Kim, (2003)	1,204	>65	South Korea	Global	MMSE	+ *
Dik, (2001)	1,168	62 – 85	Netherlands	Global	MMSE	N/A

MMSE= Mini-mental state examination, **SPMSQ=** Short Portable Mental Status Questionnaire, **CVLT=** California Verbal Learning Test, **N/A=** Not Available**, SIDAM SISCO=** Structured Interview for the Diagnosis of Dementia of the Alzheimer Type, **CERAD=**Consortium to establish a registry for Alzheimer Disease, **SIDAM=**Structured Interview for the Diagnosis of Dementia of the Alzheimer Type, **BVRT=** Benton Visual Retention Test, **WMS=** Wechsler Memory Scale, **CASI=** Scale wish contains nine domains (long-term memory, short-term memory, attention, concentration/mental manipulation, orientation, visual construction, abstraction and judgment, list-generating fluency)**, AVLT=** Auditory Verbal Learning Test
*After adjustment for age and education

V.4 Conclusions

The SMC prevalence in population based studies over 1000 subjects, ranged very widely from 4.6% to 57.3%. Most of these studies used a single question to define and identify SMC, which may have given rise to differences in findings. The selected community studies (i.e. those with sample sizes of at least 1000 subjects) report reasonably consistent associations for SMC with older age and lower education; however, associations with gender are inconsistent. Strong and consistent associations are reported between SMC and depression. Those with cognitive impairment on the other hand are inconsistent, although positive associations may be more likely to be observed for narrower definitions of SMC where reported memory difficulties are relatively severe. This literature review supports the conclusion of Abdulrab and Heun (2008) that SMCs are frequent among older people, although their prevalence and correlates do vary substantially between studies, possibly related to differences in definitions and methods of ascertainment; as well as the fact that SMC is a symptom of a range of different disorders including depression as well as early neurodegeneration.

VI.- INFORMANT MEMORY REPORTS

VI.1 Introduction, concept and definitions

There are several kinds of approaches which clinicians can use to assess cognitive impairment in their patients: cognitive testing, self-report of cognitive deficits by the patient, observation of everyday performance by staff, and informant reports of everyday cognitive functioning (Jorm, 1996).

The most explored approach has been objective cognitive assessment, whether involving brief or extended evaluations, although it may be difficult to establish at mild stages of impairment how much current function differs from lifelong ability, in addition to what impact any impairment is exerting on daily function. Self-reported cognitive function (i.e. with impairment reflected in SMC as described in the previous chapter) captures an individual's awareness of and belief about their own cognitive competence in daily life (Grut et al., 1993), particularly in relation to what the individual believes is or should be their normal function, allowing an assessment of everyday memory and cognitive problems that may not be captured by standardized neuropsychological tests, and thus providing clinicians with another perspective of understanding memory and cognitive function in old age (Chung and Man, 2009). However, not all people will be willing or able to recognise and/or report objective deficits.

Lack of insight concerning cognitive and functional deficits is a symptom in many neuropsychiatric disorders. Different terms have been used to describe the phenomenon, including anosognosia, unawareness of deficits, and lack of insight (McGlynn and Schacter, 1989). Anosognosia is not a unitary construct, and various approaches have been taken to develop methods for assessment of awareness. Most of these have limitations (Claire, 2002)

and no "gold standard" test for examining insight exists, which complicates the comparability of different studies (Vogel et al., 2004). Four main approaches have been taken in assessing the level of awareness:

a. Evaluation by a clinician (Lopez et al., 1994, Reed et al., 1993)

b. Discrepancies in scores on parallel version of rating scales or questionnaires given to the patient and a close relative (Michon et al., 1994, Vasterling et al., 1997)

c. Discrepancies between patient self-ratings and their scores on objective memory tests (Dalla Barba et al., 1995)

d. Combinations of the above (Clare et al., 2002).

Evaluation by a clinician is by far the most commonly used method for assessment of awareness; however, few studies have examined if the use of additional methods provides useful information not elicited by short categorical stratifications (Vogel et al., 2004). Knowing the potential limitations of self-reported information, informant reports have been used as a complementary source of information about memory and other domains of cognitive function in older people, and have been suggested to be more robust in differentiating individual with normal cognition from those with dementia and in predicting future incidence of dementia (Carr et al., 2000).

In community-based dementia studies, researchers have often combined the two approaches to augment the discriminating ability of dementia diagnostic schedules although previous studies have found that informant reports performed equally as well as cognitive assessment in this respect (Law and Wolfson, 1995, Hall et al., 1993, Cacchione et al., 2003,

Knafelc et al., 2003, Mackinnon et al., 2003, Mackinnon and Mulligan, 1998, Slavin et al., 2010, Tierney et al., 2003) (Table VI.1)

There are now a wide range of validated informant instruments for screening and assessment of dementia (Jorm, 1996). A meta-analysis of studies comparing an informant instrument with a brief cognitive test found that informant scales perform as well as cognitive screening tests (Jorm, 1997) meaning that the cognitive performance tests have validated the informant report. Pooled data from 10 studies showed that informant scales had a sensitivity of 86% and a specificity of 80%, compared with a sensitivity of 79% and specificity of 80% for brief cognitive tests.

Although head-to-head comparisons of the two approaches are informative, in actual clinical practice, they should be viewed as complementary rather than competing, and each approach has strengths and weaknesses relative to the other. Tierney (2003), for example, found that the inclusion of informant ratings with the MMSE significantly improved its accuracy in the prediction of probable AD, although this finding required replication.

For informant-based screening measures, strengths include (Jorm, 2003).

a) Relevance to everyday cognitive functioning. Informant-based measures draw upon the cognitive demands of a person's everyday life, in contrast to cognitive screening tests, which rely on a standard set of artificial tasks.
b) Cultural fairness. Level of education and cultural background are known to influence cognitive tests. Level of education affects informant-based measures much less, and informant based measures may have greater cross-cultural

portability because they assess aspects of everyday life that are common to many cultures (e.g. remembering people's names)

c) Direct assessment of change. In screening for dementia, it is important to know that a given degree of cognitive impairment reflects a deterioration from normal function; however, serial cognitive assessments are seldom feasible, and clinical decisions must be made on the basis of cross-sectional assessment. With informant-based measures, the informant knows about the patient's earlier functioning and can retrospectively report on cognitive change.

d) Acceptability to patients. Cognitive assessment can be an unpleasant experience for a patient because it draws attention to their deficits. By contrast, informant-based measures do not require the patient to demonstrate cognitive failures.

Balanced against these advantages one of the major limitations is that patients or participants will sometimes lack a suitable informant, particularly if a longitudinal perspective is required. Another weakness is that some informants will provide less valid accounts than others. Nevertheless, relatively little is known about the influence of informant characteristics on validity (Jorm, 2003, Jorm, 1996), although those that have been identified include less accurate reports from informants who do not live with the patient, who have seen them relatively infrequently, and who are older and less educated at the time of questioning. These informants tend to overestimate the patient's capabilities. The caregiver in addition may be more or less aware of the index person's behavioural and functional disorders. This subjective perception is influenced by the clinical presentation, by the presence of different symptoms and their severity, by the degree of kindred and

family ties, and by caregiver factors such as time dedicated to the patient, psychological status, knowledge of the illness, and cultural and professional status (Onor et al., 2006).

VI.2 Informant memory report studies in MCI and dementia

The most of the studies in MCI and dementia that have evaluated informant-reported cognitive impairment have been done recently in high-income countries, with small sample size, clinical settings (few of them in the community); and using a variety of informant report instruments. Studies evaluating informant report measures are displayed descriptively in Table VI.1

Artero (2003) concluded that tests supplemented by information from proxies and observations may detect prodromal cognitive disorder or MCI. In the other hand Onor (2006) reported the perception of cognitive, behavioural and functional problems in MCI and AD patients, finding that these perceptions are more affected in AD patients than in those with MCI. Another observation was that subjective reports were not associated with decrements in memory while informant and clinician report had a positive association (Frerichs and Tuokko (2006)

Table V1.1 Summarizing studies which have evaluated the usefulness of informant reports in people with MCI or dementia

Author (year)	Participants	Country	Setting	Dx criteria	Instrument for informant report	Functions evaluated (proxy)	Other measures	Objectives	Findings
Artero (2003)	308 SCC confirmed by proxy (no DSM-III dementia) 60 without cognitive complaint	France	General Practice	Ritchie, 2001	DECO	Activity level semantic and visual memory, memory of places, events and procedures visuo-spatial performance new skill learning	Cognitive test battery ("Examen cognitif par ordinateur Echelle comportement et adaptation")	Construct guidelines for MCI detection	Tests supplemented by information from proxies and observations may detected prodromal cognitive disorder or MCI
Onor (2006)	60 MCI 61 mild AD	Italy	Unit of clinical Psychiatry	MCI Petersen AD DSM-IV	SAI, CIRS	Measures of insight, global score and insight in 4 dimensions	MMSE NPI ADL IADL	Compare the perception of cognitive, behavioural and functional problems in persons with MCI and AD	
Hanyu (2007)	44 MCI, 37 AD	Japan	Unclear	NINCDS-ADRDA and Petersen	EMC Memory checklist	Cognitive competency	MMSE	Examine the level of awareness of memory deficits between MCI vs AD	MCI and AD patients showed impairment awareness of memory deficit
Vogel (2004)	36 mild AD, 30 aMCI and 33 controls	Denmark	Memory Clinic	NINCDS-ADRDA and Petersen	ARS and MQ	Memory questioner for patient and relatives + semistructured interview that evaluate insight in 4 dimensions	DART, MMSE, CCR, Wisconsin, Stroop, Trail Making	Assess awareness in patients with aMCI vs AD and controls	No significant differences in awareness between MCI and AD
Frerichs and Tuokko (2006)	229 NCI	Canada	Community study	Consensus panel DSMIII-R	Section H of CAMDEX	Questions about Remembering recent events	BCR	To examine the relation between the change in memory test performance and self and informants report and clinician judgment	Subjective reports were not associate with decrements in memory, informant and clinician report had a positive association

DSM-III= Diagnostic and Statistical Manual of Mental Disorders**, AD=** Alzheimer disease, **MCI=** Mild cognitive impairment, **NPI=** Neuropsychiatric Inventory**, ADL=** Activities of Daily **IADL=** Inventory Activities of Daily Living**, DSM-IV=** Diagnostic and Statistical Manual of Mental Disorders IV**, DECO**= Deterioration Cognitive Observed, **NINCDS-ADRDA=** National Institute Of Neurological and Communicative disorders and Stroke and the Alzheimer Disease´s and Related Disorders Association**, MMSE=** Mini-mental state examination**, MQ=** Mindfulness Questionnaire, **DSMIII-R=** Diagnostic and Statistical Manual of Mental Disorders III Review**, CAMDEX=** Cambridge Mental Disorders of the Elderly Examination

VI.3 Informant memory report and cognitive functioning

Informants have been shown to be a reliable and a valid source of information in determining the presence of DAT, even in the mild stages. Carr et al testing the value of informant versus individual´s complaints of memory in early dementia, reported that informants were better in distinguishing subjects with and without dementia as judged by the clinician (Carr et al., 2000). Recently Potter et al (2009), compared direct testing (CERAD) and informant-reported of cognition (IQCODE) with clinical diagnosis of cognitive impairment and dementia in African American and white American samples and they found higher IQCODE scores associated with increased odds of dementia to a similar extent in both groups, but for cognitive impairment as an outcome the association was found only for the white American sample.

VI.4 Informant memory report and subjective memory complaints

Few studies have investigated the degree with which informant-reported and self-reported cognitive/memory impairment are correlated. One study (Farias et al., 2005) found that self- and informant-reported everyday memory and cognitive functioning were similar in MCI and normal controls, but differed in those with a dementia diagnosis, because in the last case the subjects affected did not recognize their cognitive impairment.

Some people with MCI may show signs of diminished awareness of their memory and/or cognitive function, as suggested by informant reports and neuropsychological assessment (Chung and Man, 2009, Onor et al., 2006) identified major differences between how people with MCI or mild AD and their caregivers perceived the index person's cognitive and

behavioural disorders; the group with MCI or mild AD were found to underestimate their deficits, which were considered serious and disabling by their caregivers.

In the Sydney Memory and Aging Study (Slavin et al., 2010), participants reported more memory complaints than informants reported problems, but there was weak agreement between participants and informants on the complaints themselves. The authors concluded that informant-based complaints may more accurately reflect cognitive status because a higher prevalence of informant complaints was found in participants who had objective cognitive impairment, and informant complaints were more strongly correlated with performance on neuropsychological testing. However, these correlations were still relatively small) and complaints were found to be common so it was concluded that both subjective and informant-reported impairment are likely to be influenced by a number of psychological factors besides observed cognitive function.

From a French sample, it was concluded that approximately 50% of the population aged 65 and over reported subjective cognitive deficits which were confirmed by proxies (Ritchie and Fuhrer, 1992).

VI.5 Validity of informant reports

Validation studies for informant reports of cognitive decline tend to have had better methodological design than studies of SMC and to use more similar instruments between them such as CAMDEX and IQCODE (Table VI.2). The accuracy of these informant evaluations have been assessed by investigating associations with standard screening tests, the most used being the MMSE. Only two of the revised studies were population based (Makinon and Fiske), the rest being carried out in clinical populations.

Carr (2002) found that informants were successful in distinguishing normal subjects from those with dementia and Tierney (1996, 2003) found that informant's perceptions contributed significantly to the prediction of AD and that the inclusion of informant ratings plus MMSE significantly improved the prediction of probable AD. This was supported by Mackinnon (2003) who pointed out that appropriate combination of existing tests may be a fruitful method of improving screening accuracy.

Finke´s study (2005), concluded that informant reports of dementia onset are reliable and reasonably valid but, on the other hand, Kemp (2002) reported that 40% of informant reports are inaccurate – particularly when the patient has low education.

Table V1.2 Studies investigating the relationship between informant reports and cognitive impairment and/or dementia risk

Author (year)	N	Country	Population	Instrument	Measure	Information Source	Findings
Carr (2000)	158 CDR-W 0 165 CDR-W 0.5 159 CDR-W 1	USA	AD research centre		Clinical dementia rating scale Washington	Subjects Informants	Informants were successful in identifying normal subjects and those with dementia
Tierney (1996)	120 memory impaired patients without DSM III dementia	Canada	Reference centres Research program in Aging	CAMDEX	MMSE Wechsler memory scale California Verbal learning tests Boston naming test WAIS	Subjects Informants	Informant's perceptions contributed significantly to the prediction to AD.
Tierney (2003)	165 subjects without DSM III dementia	Canada	Reference centres	CAMDEX	MMSE	Subjects Informants	Inclusion of informant ratings + MMSE significantly improved the prediction of probable AD
Perroco (2009)	37 subjects mild.moderate dementia 57 ND	Brazil	Psychiatry clinic	IQCODE	MMSE	Patients Informants	IQ code is not biased by schooling
Kemp (2002)	248 community dwelling patients	Australia	GP	CAMDEX Lawton Brody	MMSE CAMCOG	Subjects Informants	40% of informant reports are inaccurate particularly when the patient has low education
Mackinnon(2003)	646 subjects	Australia	Population based	IQCODE	MMSE	Subjects Informants	Appropriate combination of existing tests may be a fruitful method of improving screening accuracy
Fiske (2005)	297 dementia patients	Sweden	Population based	Semi-structured interview Harmony	Semi-structured interview Harmony	Subjects Informants	Informant reports of age of dementia onset are reliable an reasonably valid

CDR-W= Clinical Dementia Rating, **AD=** Alzheimer Disease, **CAMDEX=** Cambridge Mental Disorders of the Elderly Examination, **MMSE=** Mini-mental state examination, **WAIS=** Wechsler Adult Intelligence Scale, **DSM III=** Diagnostic and Statistical Manual of Mental Disorders III, **IQ=**Intelligence Quotient, **CAMCOG=**Cambridge Cognitive Examination , **GP=** General Practitioner, **CDR=**Clinical Dementia Rating, **SMC=**Subjective Memory Complaints

VI.6 Conclusions

Despite longstanding clinical practice of assessing dementia and mild cognitive impairment through cognitive assessment supplemented by information provided by informants, there is a lack of research into this combination of data and a lack of standardized informant instruments. In the assessment of cognitive impairment and dementia the use of informant reports provide several advantages including the opportunity to evaluate everyday cognitive performance, more acceptability than cognitive testing, a longitudinal perspective, retrospective evaluation, evaluations where cognitive assessment is not feasible, and evaluations using different forms of communication (e.g. face-to-face, by mail, by telephone). However, limitations have to be taken in account including difficulties in finding a suitable informant, or where there are requirements to evaluate specific cognitive functions. In the context of international studies, cultural differences may influence informant reports of prevalent CIND and dementia, and there is a need for more comparative research to establish the cultural validity of this construct (Potter et al., 2009)

VII. - STUDIES INVESTIGATING THE ASSOCIATION BETWEEN COGNITION AND DISABILITY.

VII.1 Introduction, functional capacity and disability

Functional capacity represents a wide range of everyday skills and abilities that are necessary for independent living within the home and community. These skills range from routine activities of physical self-care through to more cognitively complex behaviours such as financial tasks, use of transportation, and medication management (Marson D and Hebert K 2006).

Although cognition has influences across this range of simple to higher-order functional activities, it also remains conceptually and analytically distinct from them. Functional incapacity in older people may occur with or without corresponding decline in cognition. Impaired sensory processes, acute or chronic medical illness, or any other physical limitation or injury affecting strength, balance, mobility, concentration, and endurance may adversely impact functional performance (Lowenstein and Mogosky, 1999). At the same time, it is important to bear in mind that a large proportion of functional decline in the elderly is intimately linked to cognitive impairment and that one of the most important risk factors for functional decline in older adults is the presence of a neurodegenerative disorder such as Alzheimer disease the prevalence of which increases dramatically with age and where functional decline is a required diagnostic criterion. As such, reliable and valid measures of functional ability are essential to diagnoses of dementia.

MCI diagnostic criteria generally stipulate that functional capacity is preserved in order to distinguish this entity from dementia. Nevertheless, functional capacity will decline gradually with worsening cognition without a discrete point where this suddenly occurs. The supposed absence of functional decline in MCI may represent a true preservation of

functional abilities in the face of clinically significant memory loss; however, it may also reflect insufficiency of objective measures or expertise to detect subtle prodromal changes in functional performance at different degrees and domains of cognitive impairment.

Activities of daily living (ADLs) and instrumental activities of daily living (IADLs) exist on a functional continuum and primarily reflect a method of categorization rather than independent constructs (Wolinsky and Tierney, 1998). This arbitrary classification is based on distinguishable levels of functionality that are hierarchically related and differentiated by their degree of cognitive complexity and their pattern of acquisition, loss and recovery (Lowenstein and Mogosky, 1999, Olver et al., 1996, Stern et al., 1990).

ADLs typically include elemental activities for self-care such as washing, feeding, dressing, toileting and moving. IADLs on the other hand represent more complex activities from a broader range of higher level tasks, including shopping, using the telephone, housekeeping, preparing food, doing the laundry, using various types of transport, managing medication, or managing finances.

VII.2 Evaluating functional status and disability

The capacity to function independently is poorly described by the constellation of medical disorders alone. Similarly, performance on mental status testing does not necessarily predict functional status. Functional status should instead be evaluated independently of medical and cognitive assessments. The concept of disability clearly plays a crucial role in defining which measurement of disability will be adopted (Sousa et al., 2010). Measurements of disability are important for the design and provision of services, for

monitoring the levels of functioning in a population and their impacts, for evaluating interventions to prevent or minimize limitation and restrictions, and for evaluating the equalization of opportunities (Mont, 2007)

Evaluation of functional status is not limited to the assessment of specific activities and tasks; this kind of assessment may also include significant events in a person's life or family that have a bearing on the health status or situation (events of daily living), demands placed on the person from within or from the family or society (demands of daily living), the nature of the physical environment (environment of daily living), and the person's values and beliefs that determine decisions and responses regarding health care (values and beliefs in daily living).

According to some authors, functional disability can be measured through 'independence difficulties' scales; usually these can take three forms: severity of difficulties in performing certain activities, need of assistance, and degree of dependence to perform activities. A measure of dependence evaluates if a person needs help or assistance to perform an activity. A person is classified as dependent when he/she absolutely needs help to achieve some goals. On the other hand a dependence scale could help to tell us the real need of help of a person and to plan strategies to the future. The most widely used approaches to measuring functional disability in the literature are as follows:

- A single question about self-reported "disability"
- A check-list of common chronic diseases or impairments
- Enquiry about basic activities of daily living (ADL)
- An instrumental activities of daily living (IADL) scale

- Mobility
- Specific functions (dressing, walking.)
- Specific illness
- Health status questionnaires

These indicators can be evaluated by means of the degree of difficulty and/or by means of the degree of dependence.

There are many instruments for assessing ADL and IADL (Table VII.1), and can be classified into reports (self-report; informant report) and direct assessment methods (performance-based or clinician rating measures). Self- and informant-reports are the most commonly used methods. These involve the individual or (more typically) a caregiver or other knowledgeable informant (i.e., proxy) to provide ratings of the index individual's ability to perform basic self-care and complex instrumental activities at home and in the community (Marson D, 2006). Self- and caregiver judgments of functional ability suffer a number of limitations (Wadley, Harrel & Marson, 2003; Wild & Cotrell, 2003), but are still commonly used because of their minimal cost and relative ease and brevity of administration and scoring (Lowenstein and Mogosky, 1999) (Angel & Frisco, 2001). Self-reported measures of physical disability assess difficulty, inability or degree of assistance required to perform specific tasks of mobility, household management or personal care. However, because people with preclinical disability due to impairment are still able to accomplish a task under certain circumstances without perceiving a difficulty, the above measures may not be sensitive enough to recognize early functional decline. An effective self-report measure was developed to identify individuals in the pre-clinical stage of

disability by focusing on modification of usual methods of performing mobility tasks, which compensate for the impact of underlying health changes. On this instrument, self-reported task modification and performance measures were found to be independent and strong predictors of incident mobility disability (Gibson et al., 2010)

Disability has therefore been assessed with a wide variety of instruments; however, even when instruments contain the same items, they may differ in how they assess specific aspects of performing the task or the severity of limitation in performing the task. There is no single best way to perform a disability assessment, and there is no single instrument that is ideal. Moreover, the lack of standardization that results from the use of multiple competing instruments makes it difficult to compare prevalence's of disability between studies(Ferrucci et al., 2008). Aiming to generate an ideal and universal adopted instrument to measure health and disability, the WHO developed the Disability Assessment Schedule 2.0 (WHODAS 2.0) which has several convenient characteristics: it has been constructed to follow the ICF classification and has been proved to be reliable and valid across different populations and cultures, maintaining unidimensionality (with one single global disability latent trait) and discriminatory validity (Sousa et al., 2010).

Table VII.1 Instruments for assessment of ADL in people with MCI or dementia

Autor - year	Instrument	Time taken	Rating	Indications
Resiberg, B (2001)	ADL-IS	30 min.	Caregiver completed	An activities of daily living scale for pharmacological or other therapeutic trials in Alzheimer disease and related dementing disorders
Cullum CM (2001)	The Texas Functional Living Scale	15 – 20 min.	By experienced interviewer	To measure functional abilities in dementia
Gelinas (1999)	DAD	15 min.	By trained interviewer	Assessment of functional disability for use of careers of community
Hindmarch (1998)	B-ADL	20 min.	By caregiver	Assessment of activities of daily living people with mild to moderate dementia
Galasko (1997)	ADCS ADL	20 min.	Informant based	Assessment of ADL in patients with Alzheimer Disease with particular reference to outcomes in clinical trials
Bucks (1996)	BADLS	15 min.	By career	Assessment of ADLs in patients With dementia
Burns (1994)	Cognitive Performance Test	45 min.	By trained interviewer	Assessment of functional capacity in dementia
Tappen (1994)	RADL	20 min.	By nurses	Designed specifically for patients with Alzheimer disease in the middle and later stages of the illness
Stern (1994)	Dependence Scale	5 min.	Trained interviewer asking caregiver	A structured scale developed for longitudinal studies of Alzheimer dementia, to rate the degree of dependency of or assistance needed by a patient
Hall (1993)	CSID	30 min.	By trained interviewer	Screening for dementia
Patterson (1992)	CSADL	25 min.	By primary caregiver, by nurse, clinician or trained interviewer	Assessment of ADLs in Alzheimer disease
Mahurin (1991)	SAILS	60 min.	By trained interviewer	Assessment of everyday activities affected in dementia
Loewenstein (1989)	DAFS	25 min.	By Trained interviewer	Direct assessment of functional capacities in AD patients
Moore (1983)	FDS	15 min.	By careers	Instruments used by families to monitor functional disability in dementia
Linn (1982)	RDRS-2	10 min.	Anyone who knows the subject, preferably with one training session	To assess disability in elderly people
Reisberg (1988)	FAST	2 min.	By clinician after interview with informant	Assessment of functional change in ageing and dementia
Hughes (1982)	CDR	40 Min.	By a clinician using information gathered as part of clinical practice	Global measure of dementia severity
Gottfries (1982)	GBS SCALE	30 min.	By trained observer	To rate the degree of physical inactivity impairment of intellectual and emotional capacities and behavioural

Autor - year	Instrument	Time taken	Rating	Indications
				symptoms common in dementia
Reisberg (1982)	GDS	2 min.	By clinician	Staging instrument indicating deterioration in dementia
Wilkinson (1980)	PGDRS	20 min.	By staff	Measure of dependency in elderly patients
Sheikh (1979)	ADL index	10 Min.	By observer	Assessment of daily living function in chronic disability
Kuriansky (1976)	PTADL	20 min.	By experienced interviewer	To measure self-care capacity in late-life mental disorders
Meer (1966)	SGRS	10 – 15 min.	By nurse career	Rating of needs based on behaviour physical and mental functioning

ADCS ADL = Alzheimer's Disease Cooperative Study Activities of Daily Living; **ADL** = Activities of daily living; **ADL-IS** = Activities of daily living international scale; **BADL** = Bayer Activities of Daily Living Scale; **BADLS** = Bristol Activities of Daily Living Scale; **CDR** = Clinical Dementia Rating; **CPT** = Cognitive Performance Test; **CSADL** = Cleveland Scale for Activities of Daily Living; **DAD** = Disability Assessment for Dementia; **DAFS** = Direct Assessment of Functional Status; **FAST** = Functional assessment staging; **FDS** = Functional Dementia Scale; **GBS** = Gottfries, Brune and Steen scale; **GDS** = Global Deterioration Scale; **PGDRS** = Psychogeriatric dependency rating scales; **PTADL** = Performance Test of Activities of Daily Living; **RADL** = Refined Activities of Daily Living Assessment Scale; **RDRS** = Rapid Disability Rating Scale; **SAILS** = Structured Assessment of Independent Living Skills; **SGRS** = Stockton Geriatric Rating Scale; **TFLS** = Texas Functional Living Scale

VII.3 Aetiology of disability in the elderly

It is important to bear in mind that disability has a multi-factorial aetiology with complex interactions between the person and their environment (Sousa et al., 2010). Longitudinal studies in older populations have revealed the presence of multiple risk factors for disability, as well as illustrating the dynamics of disability onset and progression. As described earlier, disability is a product of the disease or diseases from which an individual suffers, a sedentary lifestyle or disuse, and physiologic declines that may themselves be the result of normal or accelerated ageing processes – not necessarily specific diseases but rather factors potentially influencing 'frailty' such as inflammatory or endocrine changes. These predisposing conditions may have an impact on the initiation of disability and on changes in the status of already established disability (Ferrucci et al., 2008).

VII.4 Disability and cognition (dementia, MCI)

Dementia is one of the major causes of disability in later life. The individual impact of dementia on disability involves a circular argument, since adverse effects of cognitive decline on function is a diagnostic criterion. However, the impact of dementia on disability and at a societal level is now increasingly recognized – both in terms of disability itself as an outcome and in terms of its economic consequences. The disability weight for dementia applied in the Global Burden of Disease report was higher than that for almost any other condition with the exception of spinal cord injury and terminal cancer. Among older people, dementia was the most burdensome neuropsychiatric disorder accounting for more than half of all disability adjusted life years in this domain of morbidity. People with dementia are heavy consumers of health services, but in developed countries most direct costs arise from community and residential care. In North America High Income, the total annual cost for dementia in 2010, was $213.04 billions (US$); for Europe Western $210.12 billions (US$); Latin America Central $6.56 billions (US$); for Asia Central $0.94 billions (US$); Africa Central $0.07 billions (US$); (ADI Report 2010) The economic burden is unevenly distributed; families from the poorest countries are particularly likely to use expensive private medical services and to be spending more than 10% of per capita GNP on health care. Worldwide, family caregivers are the cornerstones of support for people with dementia. They experience significant psychological, practical and economic strain. Dementia care is particularly time intensive because of the need for close supervision. Many caregivers need to give up or cut back upon work in order to care. (WHO, 2009).

As described earlier, dementia exists on a continuum of cognitive function. Relationships between cognition and disability are potentially complex to elicit when categories such as

dementia or MCI are applied because the presence or not of a given level of disability is used to define such categories. Nevertheless, a considerable body of research has examined the relationship between cognitive abilities and ADL/IADL functional performance, with particular reference to older adults. Cognitive ageing studies have addressed the relationship of functional performance to different and specific cognitive functions, and performance on various standardised psychometric measures for several mental functions (Marson D, 2006). In the remainder of this chapter, some representative studies in these areas will be considered in terms of the cognitive function continuum (cognitive aging, MCI and dementia).

VII.4.1 Functional status and dementia studies.

Because functional decline is necessary for a dementia diagnosis, it is not surprising that the literature is substantial and uncontroversial. Cognitive and functional changes in dementia are closely linked but with a reasonable degree of heterogeneity. For example, in a longitudinal study of people with dementia, Mortimer et al. (1992) found that only 40% of the variance in functional decline was accounted for y cognitive decline, suggesting that cognitive and functional capacity may reflect distinct yet parallel features of the disease process. Furthermore, they found that rates of cognitive and functional decline differed substantially with regard to neuropsychological predictors. Lower baseline scores on verbal tests of confrontation naming, learning and recall, fluency, abstraction, and immediate memory emerged as key predictors of faster rates of functional decline. Different predictors of functional and cognitive decline again suggest that they are distinct constructs in dementia (Marson, 2006). Global mental status measures, particularly neuropsychological measures of executive function, have been found to account for a significant portion of the

variance in ADL and IADL function. Taking a broader view, deficits in higher-order cognitive abilities have been found to correspond with difficulty in performing complex tasks of everyday living even in the preclinical stages of dementia (Griffith et al., 2003); however, as the disease progresses more general measures of global cognitive function emerge (Grigsby et al., 1998).

VII.4.2 Functional status and MCI studies

According to MCI diagnostic criteria, individuals in this state do not present significant changes in their ADLs (Petersen et al., 1999). This point is a critical issue, because once functional decline is detected the diagnosis begins to shift from MCI to dementia. Thus under the Mayo criteria, people with MCI have been described as having "usually intact" ADLs (Ritchie et al., 2001) or "only slightly abnormal" ADLs (Petersen et al., 1999). Guidelines for functional change in MCI have been suggested to be vague and unsatisfactory as diagnostic criteria (Ritchie et al., 2001), and as probably reflecting currently limited empirical knowledge concerning the types and extent of functional change that occur in MCI (Marson D, 2006). Despite these problems with the diagnosis, emerging evidence does indicate that MCI is associated with at least some impairment in daily function (Daly et al., 2000, Ritchie et al., 2001, Morris et al., 2001, Touchon and Ritchie, 1999, Tabert et al., 2002, Albert et al., 1999) and directly assessed aMCI was associated with mild impairments in higher-order financial skills (Griffith et al., 2003).

VII.4.3 Functional status in cognitive ageing studies.

Several studies have also examined the association between cognitive and functional decline in what is termed 'normal ageing' (Barberger-Gateau et al., 1999, Mortimer et al., 1992, Willis et al., 1992). In a longitudinal study of community-dwelling older adults (Willis et al., 1992), performance of measures of fluid intelligence, crystalized intelligence, and processing speed declined significantly over a 7-year period, as did performance on a measure of everyday task competence. Fluid reasoning ability emerged as the strongest longitudinal predictor of everyday task competence (accounting for 52% of the variance), as compared to crystalized intelligence (11%), processing speed (6%), memory (less than 1%), age (5%) and education (6%). Interestingly, only 38% of the sample demonstrated significant longitudinal declines in everyday task competence, and this percentage was equivalent to the proportion of individuals who had significantly reduced fluid reasoning ability (37%) (Willis et al., 1992). The authors concluded that changes in functional performance are not the direct result of advancing age *per se* but instead are linked to a concurrent decline in those cognitive abilities that underlie everyday task competence.

VII. 5 Conclusions

Although functional and cognitive decline are separately measured, a large proportion of functional decline in the elderly is potentially attributable to cognitive decline and one of the most important risk factors for functional decline in older adults is the presence of a neurodegenerative disorder such as Alzheimer disease, the prevalence of which increases dramatically with age. Investigations of associations between dementia, MCI and functional decline are complicated by the fact that functional impairment is incorporated into the criteria used for defining both cognitive diagnoses. However, studies outside these groups

in so-called ‘normal ageing’ support a role for level of cognition in the aetiology of functional impairment.

As an underlying issue, in this review it was evident that a wide variety of instruments have been used to investigate disability in older populations, with differences in underlying constructs being measured (e.g. IADL, ADL), in durations of instruments (2-60 minutes) and in the ratters (self, caregivers, experienced interviewers, nurses or clinicians). This lack of standardization from the use of multiple competing instruments makes it difficult to compare disability prevalences between studies (Ferrucci et al., 2008). The WHO Disability Assessment Schedule 2.0 (WHODAS 2.0) offers some potential for a more standardized approach, having found to be unidimensional, reliable and valid across different populations and cultures (Sousa et al., 2010).

VIII. -SUMMARY OF THE BACKGROUND LITERATURE

Population ageing will have profound impact on a broad range of economic, political and social conditions. In many less developed regions of the world, the older population is growing at a much faster rate than has been observed in developed nations. In the last fifty years the rates of increase have tended to decline in the more developed regions and to increase in developed regions.

In parallel with these demographic changes an epidemiological transition is taking place from a burden of disease dominated by mortality from infectious causes to degenerative or chronic causes – currently being experienced in low- and middle-income countries is compressed into a shorter time frame than that experienced historically in high-income countries.

Dementia, as an age-associated condition, is at the forefront of this transition, having a substantial impact on years lived with disability and mortality. In order to develop preventive interventions, it is important to identify the early stages of cognitive decline, but very little research has been carried out into this in low and middle-income countries, despite the rapid expansion in need.

Research into cognitive aging and dementia is focusing increasingly on the characterization of the earliest stages of cognitive impairment, and a variety of clinically-defined pre-dementia syndromes with differing diagnostic criteria and nomenclature, have been proposed to describe non-disabling but symptomatic cognitive deficits arising in elderly persons.

In 2001, Petersen proposed the following criteria: (1) memory complaint preferably corroborated by an informant; (2) objective memory impairment; (3) normal general cognitive function, (4) intact activities of daily living, (5) no dementia. While MCI and a sub-category amnestic MCI (aMCI) have been used extensively in clinical research settings, their application in epidemiological samples has been more problematic, with surveys showing considerable heterogeneity in findings because of methodological sources of variability such as case definition, instruments used for evaluating cognitive functioning, differences in the populations studied and the different methods used to analyse and present results. Several studies however have consistently found a positive association of MCI with age and depression.

Key constructs underlying MCI are subjective memory complaint (SMC), informant-reported memory deficit (IMD) in relation to objective cognitive function. An additional important component is the relationship between cognitive impairment and disability since the differentiation between MCI and dementia rests on the presence or absence of significant disability.

Older people frequently report sMCs, although the prevalence varies considerably, depending on how it is ascertained and associations with objective cognitive impairment have not been consistent in community samples. However, despite this controversy, SMC has potential clinical importance because it constitutes a common reason for help-seeking behaviour and/or secondary care referral

Even though clinicians ascertain cognitive decline routinely through information provided by informants, there is a lack of research into this as a measure. International studies indicate potential cultural influences on informant reports of cognitive impairment and/or dementia.

Functional disability in the elderly may occur with or without corresponding decline in cognition. At the same time, it is important to bear in mind that a large proportion of functional decline in the elderly is intimately linked to cognitive impairment and that dementia is one of the most important risk factors for functional decline in older adults. MCI and related constructs tend to specify that functional capacity is preserved using this criterion to distinguish them from dementia. Nevertheless, it remains unclear whether this absence of functional decline in MCI patients is a true preservation of functional abilities in the face of clinically significant memory loss or simply reflecting a lack of sufficiently sensitive measures to detect subtle prodromal changes in functional performance associated with impaired cognition.

IX. – AIMS AND OBJECTIVES

The main goal of this series of analyses using data from a coordinated programme of surveys of older people in low/middle income countries, the 10/66 studies, was to describe the prevalence of amnestic mild cognitive impairment and to analyse its underlying constructs.

The specific objectives were as follows:

1. To generate site-specific norms for the cognitive test battery used in the 10/66 studies (comprising tests of general cognitive function, verbal fluency and immediate and delayed verbal recall) and to investigate the degree and consistency across sites of associations with sociodemographic factors.

2. Operationalizing Mayo Clinic criteria for amnestic MCI (aMCI), to describe its prevalence by age, gender, education and socio-economic status in the 10/66 survey sites, to investigate cross-sectional associations with disability and neuropsychiatric symptoms and to investigate the consistency of these associations between sites.

3. To describe and compare between sites the prevalence of subjective memory complaints (SMC) and associations with dementia and with cognitive function in participants without dementia.

4. To describe and compare between sites the prevalence of informant reported memory deficits (IMD) and associations with dementia, with SMC and with cognitive function in participants without dementia.

5. To describe and compare between sites the association between cognitive function and informant-reported disability in participants without dementia.

X. - CORE METHODS

X.1 Introduction and chapter plan

This chapter describes the general methodology for the 10/66 Dementia Research Group population-based surveys, of relevance to each of the analyses presented in the subsequent five results chapters (XI to XV). The full protocol will be described in detail with a focus on the measurements used for analyses in this thesis. Statistical approaches will then be described in detail within each results chapter.

X.2 The 10/66 surveys – design and settings

The 10/66 Dementia Research Group studies are cross-sectional, comprehensive, one-phase, catchment area population-based surveys, which were carried out between 2003 and 2005. The full 10/66 population-based study protocols had been published in open access format (Prince et al., 2007). The primary sampling and recruitment waves of this study were undertaken in eleven geographically defined catchment area sites in seven countries (India, China, Cuba, Dominican Republic, Venezuela, Mexico, and Peru). The target sample size for every country was 2000–3000 participants (generally 2000) in each of the ten countries. Recruitment in China, India, Peru, and Mexico was split between urban and rural sites; all other countries included urban sites only. Most of the analyses described in this thesis are derived from these sites alone. However, several subsequent surveys have been completed and the aMCI prevalence analyses described in Chapter XII included data from a recently completed survey in Puerto Rico in which the same protocol was applied.

For urban catchment areas, predominantly middle-class or professional areas with high-income earners were deliberately avoided. Rural catchment areas were defined by low population density and traditional agrarian lifestyle. Catchment area boundaries were

precisely defined. Mapping was carried out to identify and locate all households, which were allocated household IDs. Households were then enumerated to identify possible eligible subjects (aged 65 and over). Age (and therefore eligibility) was formally determined on revisit for interview. For each household the genders and ages of all usual residents were recorded, with the names of those aged 65 years or over, on the census date. Household and participant details were stored in secure databases. These contained names, addresses, ID numbers, and contact details for neighbours, key informants and friends to facilitate tracing for potential follow-up.

Tables X.1 and X.2 provide descriptions of the study catchment areas as well as detailed information about the study countries based on the most up to date health and economic indicators from the World Bank (Souza, 2010).

Table X.1 10/66 catchment areas information

Site	Housing Type	Local Economy	Proximity of Primary Care Centre	Proximity to Hospital	Health Insurance Cover**
Cuba	Brick houses and apartments.	Every person in Cuba receives a pension from the government of 250 Cuban Pesos. Older people also receive a retirement pension. Cubans do not pay for education, health and housing. There is a fixed amount for electricity and water.	Less than 250 meters. There is one family doctor (General Practitioner) for every 160 inhabitants	5 to 10 kilometres or 10 to 15 minutes by public transport.	Provided through the ministry of public health and covers 100% of the population
Dominican Republic	All homes in Gazcue and Zona Colonial are made of cement, with plumbing systems, electricity, and potable water. But the conditions were very different in Villa Francisca and San Carlos where houses were comprised mostly of wood and maybe a cement floor, they were smaller houses, some even had zinc roofs. They all claimed to have electricity but on a schedule, no more than 6 hours a day. Shared bathroom between houses is common.	The majority receives a government pension, which are about 5,000 pesos a month (US$139 per month). That plus any additional income takes them to an average of US$2000 a year. Some also rely on family members to support them. It depends on the amount of people who live in the home. If the person lived alone, the household income would be very low. Never exceeding US$2000 a year. On some cases they would be earning about US$8000 a year. But this is a rare case and it implies a combined household income.	There are a few unspecialized care centres very close-by. About 10 minutes away.	The nearest hospital is in within the area or about 20 minutes away. But most people prefer to travel longer distances to go to the hospital they like the most. Often it would take them 40 minutes to get there.	Worker-employer prepayment schemes (Social Security Dominican Institute), prepaid private health insurance, self-managed insurance and private providers
Urban Peru (Lima)	Brick houses. 50% houses and 50% apartments/flats. All with plumbing system and electricity.	Commercial. Most of older people have social security (retirement governmental pension). A number of older people live in their owned home with their children.	Approximately 20 minutes by car	Approximately 1 hour by car	The public subsector comprises MINSA, the Social Security system and the health services of the armed forces and the police. Altogether, it has 51% of the country's hospitals, 69% of the health centres, and 99% of the health posts. Social security coverage was reduced from 40.7% of the economically active population in 1987 to 23.4 % in 1995. In
Rural Peru	Most houses are made of cane and plaster, adobe and some of them plywood. Majority of houses do not have plumbing system, and some do not have electricity. Roads are not paved.	Fishing and farming	Information not obtained	Information not obtained	

Site	Housing Type	Local Economy	Proximity of Primary Care Centre	Proximity to Hospital	Health Insurance Cover**
					2000, 32% of the population had no access to any subsystem.
Venezuela (Caricuao)	Apartments with running water, electricity and plumbing system.	Governmental pensions, private companies, street markets	There is one Primary Care Centre and one geriatric centre; both of them are public and close to the catchment area.	There is a public hospital approximately 1 km from the study area.	The IVSS provided services to 57%. The ambulatory network of the HSDM provides care to around 80% of the population. Large strata of the population do not have access or have restricted access to care
Urban Mexico (Tlalpan)	Most houses are made of brick and have tile roofs, with a minority made of asbestos or metal foil and a marginal made of palm or wood shingles. Most houses are equipped with potable water, with the vast majority having plumbing system and electricity.	The majority of the local economy involves provision of services to consumers and business.	The study catchment area is inside a medical complex therefore primary care centres are in walking distance from participants' home.	Same for PCC	Mexican Social Security Institute introduced family health insurance, which people may voluntarily obtain by paying a fee which is complemented with the government contribution
Rural Mexico (Tepoztlán & Huitzilac)	Most houses have no potable water and are made of adobe and wood.	Agriculture remains the main economic activity. Artisanal production of local regional products also takes place in small quantities.	Approximately from 30 minutes to 1 hour by public transport away from the nearest centre	Approximately 1 hour away from the closest general hospital	
Urban China (Beijing)	Courtyards or apartments/flats. All of them have plumbing system and electricity. The courtyards have shared toilets and self operated heating system with coal, while the apartments/flats have central heating system and independent toilets.	Most of the older people receive retirement pension from the government as they worked for companies or government organizations. Others have allowance from the governments.	Within 1 kilometre. But some of the elderly would rather go to higher-level hospitals rather than primary health centres.	Within 5 kilometres.	Two employee-based schemes (1 for government workers and 1 for pubic and private company workers)
Rural China (Daxing)	Brick houses. All of them have plumbing system and electricity. All of the houses have KANG* and/or electronic radiator to make the house warm during the	Most of the older people do not have retired pension, as they were farmers. In recent years, the government started given some allowance to those without retirement pensions. A great deal of	Every village has a village clinic, but only provide some basic medicine. The real primary health	Highest-level hospitals are usually 20 kilometres away from the houses.	Government contributes to a common fund, which covers healthcare costs, but only proportionate to the amount contributed. In 2005 coverage

Site	Housing Type	Local Economy	Proximity of Primary Care Centre	Proximity to Hospital	Health Insurance Cover**
	winter.	older people receives support from their children.	centres are usually located within 5 kilometres from the houses of the older people.		was ~ 40%.
Urban India (Chennai)	Information not obtained	Chennai has a diversified economic base anchored by the automobile, software services, hardware manufacturing, healthcare and financial services industries.	14 mini health centres of voluntary health service are located within 1 km. Government primary health centres in Chennai are located within 3 km	Main hospital is located within 6-8 km	Social insurance is estimated to cover only 4.2% of the population. Private health insurance constitute a negligible proportion (0.2%)
Rural India (Vellore)	Information not obtained	The mainstay for people in the rural areas is not agriculture but industries like weaving, beady rolling, match-stick rolling, leather, chemical	Proximity of primary health centres in Vellore will be within 2 km	Christian medical college hospital can be reached in 5 -7 km from the study area	

* KANG is a traditional long (2 meters or more) sleeping platform made of bricks or other forms of fired clay. Its interior cavity, leading to a flue, channels the exhaust from a wood or coal stove. The heat of a cooking fire may be used for maintaining comfort in cool weather. Typically, it occupies one-third to one half of the room, and is used for sleeping at night and for other activities during the day. Source: http://en.wikipedia.org/wiki/Kang_bed-stove.

** Source: WHO and PAHO

Table X.2 10/66 DRG Country Profiles based on estimates form the World Bank

	Cuba	Dominican Republic	Peru	Venezuela	Mexico	China	India
Population (millions)	11,204,735	9,952,711	28,836,700	27,935,000	106,350,434	1,324,655,000	1,139,964,932
Population age 0-14 years (% of total)	18.1%	31.8%	30.7%	30.2%	29.1%	20.5%	31.7%
Population ages 15-64 years (% of total)	70.3%	62.3%	63.5%	64.5%	64.7%	71.5%	63.5%
Population age 65 and above (% of total)	11.6%	5.9%	5.7%	5.3%	6.2%	7.9%	4.8%
Population Growth Rate (Annual %)	0.0%	1.4%	1.1%	1.6%	1.0%	0.5%	1.3%
Life Expectancy at birth (total population) (years)	79	73	73	74	75	73	64
Mortality rate, infant (per 1000 live births)*	4.8	27	22	16	15	18	52
Birth rate, crude (per 1000 people)	10	23	21	21	18	12	23
Death rate, crude (per 1000 people)	6.91	5.89	5.39	5.11	4.85	7.06	7.40
Fertility rates, total (births per woman)	1.51	2.65	2.57	2.54	2.10	1.77	2.74
GDP per capita§	$9,600	$4,576	$4,477	$11,246	$10,232	$3,267	$1,017
Health Expenditure, total (% of GDP)**	10.4%	5.4%	4.3%	5.8%	5.9%	4.3%	4.1%
Per capita government expenditure on health at average exchange rate (US$)	558	81	94	222	256	49	11
Public health expenditure (% of total health expenditure)***	95.5%	35.9%	58.4%	46.5%	45.4%	44.7%	26.2%
Out-of-pocket health expenditure (% of private expenditure on health)	91.3%	65.3%	75.3%	88.1%	93.1%	92.0%	89.9%

Net migration (migrants per 1000 population) †	-1.57	-2.4	-0.97	-0.84	-3.84	-0.39	-0.05
Administrative divisions	14 provinces and 1 special municipality	31 provinces and 1 district	25 regions and 1 province	23 states, 1 capital district, and 1 federal dependency	31 states and 1 federal district	23 provinces, 5 autonomous regions, and 4 municipalities	28 states and 7 union territories

[1] All estimates are for the year 2008 when not stated otherwise* Infant mortality rate is the number of infants dying before reaching one year of age, per 1,000 live births in a given year. Source: Inter-agency Group for Child Mortality Estimation (UNICEF, WHO, World Bank, UNPD, universities and research institutions).

§ Gross domestic product divided by midyear population. Data are in current U.S. dollars. Source: World Bank national accounts data and OECD National Accounts data files.

** Total health expenditure is the sum of public and private health expenditure. It covers the provision of health services (preventive and curative), family planning activities, nutrition activities, and emergency aid designated for health but does not include provision of water and sanitation for the year 2007. Source: World Health Organization National Health Account database (www.who.int/nha/en) supplemented by country data.

*** Public health expenditure consists of recurrent and capital spending from government (central and local) budgets, external borrowings and grants (including donations from international agencies and nongovernmental organizations), and social (or compulsory) health insurance funds. Total health expenditure is the sum of public and private health expenditure. It covers the provision of health services (preventive and curative), family planning activities, nutrition activities, and emergency aid designated for health but does not include provision of water and sanitation. Source: World Health Organization National Health Account database (www.who.int/nha/en) supplemented by country data.

¶ Out of pocket expenditure is any direct outlay by households, including gratuities and in-kind payments, to health practitioners and suppliers of pharmaceuticals, therapeutic appliances, and other goods and services whose primary intent is to contribute to the restoration or enhancement of the health status of individuals or population groups. It is a part of private health expenditure. Source: World Health Organization National Health Account database (www.who.int/nha/en) supplemented by country data.

†The difference between the number of persons entering and leaving a country during the year per 1,000 persons (based on midyear population). An excess of persons entering the country is referred to as net immigration (e.g., 3.56 migrants/1,000 population); an excess of persons leaving the country as net emigration (e.g., -9.26 migrants/1,000 population). The net migration rate indicates the contribution of migration to the overall level of population change. Source: CIA World Factbooks 18 December 2003 to 18 December 2008.

X.3. Ethical approval

The King's College London Research Ethics Committee approved by local ethical committees the 6 studies. Informed consent was sought from all participants. If a participant could not read or write, they did not sign the consent form. In such cases interviewers were instructed to sign in the consent form that the participant had assented, witnessed if possible by an independent person who could read and write; preferably the same person who acted as the informant. Informants were also requested to sign separate informant consent for their interview. Next of kin provided written agreement in case of lack of capacity to consent.

X.4 Pre-study preparation, interviewers and training

The full 10/66 protocol and assessment instruments were translated using a five stage method:

1) forward translation into the local language,
2) back translation into English,
3) back translation compared to the original English version,
4) a final consensus version then presented to panels of local older people and local experts,
5) the final version evaluated in an instrument pre-test pilot.

Participant centres were advised to employ interviewers who were graduates. In most sites health professionals such as psychologists and social workers carried out the interviews. In China and Cuba interviewers were medical doctors, working in primary care. All interviewers received full training on the 10/66 protocols, carried out by the local principal investigator and the local study coordinator.

The key elements of the training comprised:

a) overview of study aims and methodology,
b) detailed training in the clinical assessments (e.g. Geriatric Mental State, structured neurological examination, cognitive examinations),
c) general training in the fully structured interviews (informant interview, background and risk factor interview),
d) training in data handling and quality control procedures.

For the structured neurological examination and Geriatric Mental State, standard training videos in English were produced and distributed to local centres which either dubbed or used them to produce local videos in their local language.

X.5. The samples

X.5.1 Participant and informant identification

All people aged 65 years and over living in the geographically defined catchment areas were invited to participate in the study. The target sample size for each country was between 2000 and 3000 (generally 2000). Catchment area boundaries were precisely defined and marked on a map used to identify and locate all households. A census date was used to determine eligibility. The rationale for discrete catchment areas was that we were able to work with the local community to ensure continuing cooperation and high rates of participation, as well as facilitating potential follow-up, since the assembling of a cohort for prospective research was envisaged at the outset. A door-knocking strategy was used to identify all possibly eligible participants, and to allocate a unique identifier to each household. For each household, the gender and ages of all permanent residents were recorded with the name(s) of those possibly or definitely aged 65 years or over on the

census date. Age and eligibility were formally ascertained and confirmed when the research workers returned to carry out the interview.

Household and participant details were stored in secure databases which included names, addresses, study identifier (ID) numbers, and contact details for neighbours, key informants and friends to be used in the planned follow-up phase. For each participant an informant was identified to provide further information. The informant was chosen on the basis either that they knew the participant best or had spent the longest period of time with the older person. Although in most cases they were a co-resident of the older person and usually a family member, in some cases a non co-resident family member, or a friend or neighbour was better qualified.

X.5.2 Sample size calculation for the surveys

An overall sample of 2,000 for each country was chosen on the basis that it would allow the estimation of a typical dementia prevalence of 4.5% with what was felt to be an adequate precision of +/- 0.9%. Rural and urban samples of 1,000 each, where feasible, were chosen as allowing estimation of the same prevalence with a precision of +/- 1.2%.

X.6. Other quality control procedures used

In addition to the rigorous training given to interviewers, the 10/66 group produced a standardized operating procedure (SOP) manual distributed to PIs and SCs describing every element of the study protocol in detail, focusing in particular on data quality control. Quality control was primarily achieved through interview supervisions and diagnostic validation. Local SCs were responsible for vetting the early stages of data collection during fieldwork to assess for compliance with the study protocol as trained. Random reviews of

completed questionnaires were carried out by SCs looking for completeness, unusual patterns of response, and high levels of missing data. Any issues arising from these checks, and any problems in the fieldwork, were discussed during weekly meetings with the whole research team. If errors persisted through the quality control checks they were identified by the double data entry procedure and were dealt with before finalization of data entry.

X.7. Data handling

All data were coded onto paper versions of data coding sheets. The exception was in Cuba where all data were collected directly onto laptop computers using computerized Spanish questionnaires driven by EpiData (version 2.0) software. In all sites, data were double entered by a different data entry clerk using EpiData to minimize data transcription errors. The Chinese and India sites used the English version of the data entry files in EpiData. Both Spanish and English data entry files were identical, which facilitated data processing, data managing and processing.

All data cleaning, and processing of derived variables were carried out centrally at the London coordinating centre in SPSS using prepared syntax files. Distributions of all variables were carefully checked for anomalies, and range checks applied. After algorithms had been processed (see below where relevant), data were exported from SPSS into STATA for analysis.

X.8 Measurements

From the participant and informant interview, the following summary information was generated: dementia status, mental health, physical health, anthropometric data, demographic information, risk factor information relevant to dementia and chronic diseases,

disability, health-service use, care arrangements, and caregiver strain. The sections below detail the full range of assessments carried out on all participants in the 10/66 surveys. Individual measures of interest for specific analyses will be delineated in each Results chapter.

X.8.1Participant interview information

X.8.1.1 *Sociodemographic status*

a) Age of the participant was formally established during interview from stated age, official documentation, informant report, and, in the case of discrepancy, age according to an event calendar.

b) Living circumstances (from a complete list drawn up of co-residents with ages and relationships).

c) Marital status.

d) Education was grouped as follows: i) none, ii) primary not completed; Iii) primary completed; iv) secondary completed; v) tertiary completed. In addition, literacy was ascertained.

e) Religious affiliation and practice.

f) Community social activity, social support, and social network

g) Socio-economic status was calculated from the best occupation out of the participant and their spouse. Also recorded were current occupational status, income and sources of income, a household assets index (car, television, refrigerator, telephone, mains water, plumbed toilet), and food insecurity (assessed by the question “do you ever go hungry because there is not enough food to eat?”).

d) Rural or urban residence across the life course and migration between the two (as well as age at migration).

X.8.1.2 *Health Status*

a) Self-reported diagnoses or treatment for the following conditions were recorded: stroke, diabetes, hypertension, heart disease, hypercholesterolemia, TB, malaria, and cystercicosis.

b) Physical impairments: participants were asked about the presence or absence of 11 common and limiting physical impairments (arthritis or rheumatism; eyesight problems; hearing difficulty or deafness; persistent cough; breathlessness, difficult breathing or asthma; high blood pressure; heart trouble or angina; stomach or intestine problems; faints or blackouts; paralysis, weakness or loss of one leg or arm; skin disorders such as pressure sores, leg ulcers or severe burns). The total number of these was calculated and categorised into three groups (0, 1-2 and 3+).

c) Disability was measured by the second World Health Organization Disability Assessment Schedule (WHO-DAS 12), specifically developed by the WHO as a culture-fair assessment tool for use in cross-cultural comparative epidemiological and health services research

d) Direct physical assessments were made of pulse rate, systolic and diastolic blood pressure (average of two resting sitting and two standing), waist circumference, waist/hip ratio, walking test (5 meters walk, turn and return-timed and paces counted), leg length, height, and skull circumference. A brief, fully structured neurological assessment was carried out with objectified quantifiable measures of lateralizing signs, parkinsonism, ataxia, apraxia and primitive 'release' reflexes.

e) Reproductive status: women were asked about ages at menarche and menopause, and number of children

f) Specific dementia risk factors were enquired about, namely head injury with loss of consciousness, family history of dementia, previous depression.

g) Relevant lifestyle factors were enquired about, namely alcohol use (volume and frequency currently and before the age of 60), lifetime smoking (never, ever and current status and pack year calculation), diet (intake of fish, meat and fruit and vegetables; food insecurity), exercise and activity levels current and in earlier adult life.

h) Self-reported physical pain.

X.8.1.3 *Cognitive Status*

The core cognitive assessment comprised the cognitive component of the 'Community Screening Instrument for Dementia' (CSI 'D)(Hall et al., 1993) supplemented by the 10 word list-learning test from the 'Consortium to Establish a Registry for Alzheimer's Disease' (CERAD) (Ganguli et al., 1996)

The CSI 'D' is a 32-item cognitive test administered to the participant lasting about 20 minutes which is supplemented by a 26-item informant interview about the participant's daily functioning and general health (lasting approximately 15 minutes).

The CSI 'D' was used across cultures with the minimum of necessary adaptation. It was developed and first validated among Cree American Indians (Hall et al., 1993, Hendrie et al., 1993), further validated and used in population-based research (The US-Nigeria Study) among Nigerians in Ibadan and African-Americans in Indianapolis (Hendrie et al., 1995), and has also been validated among white Canadians in Winnipeg (Hall et al., 2000), and in Jamaica in conjunction with the CERAD battery (Unverzagt et al., 1999). The CSI 'D' test score distributions among those with dementia and controls, and the degree of discrimination provided were remarkably consistent across the aforementioned cultural settings (Hall et al., 2000).

Three summary scores can be generated from CSI 'D' using standard algorithms: a cognitive score (COGSCORE) comprising an item-weighted total score from the participant cognitive test; an informant score (RELSCORE) comprising an unweighted total score from the informant interview; and a discriminant function score (DFSCORE), a weighted score combining COGSCORE and RELSCORE. COGSCORE and DFSCORE have validated cut-off points for probable and possible cases of dementia. The animal naming verbal fluency task from the Consortium to Establish a Registry of Alzheimer's Disease (CERAD) can also be extracted from the cognitive test component of CSI 'D' (but is given little weight in COGSCORE), in which participants are asked to name as many different animals as they can in one minute.

The CERAD ten-word list-learning task was adapted for the purpose of the 10/66 surveys. Six words were taken from the original CERAD English language list: butter, arm, letter, queen, ticket, and grass. The items pole, shore, cabin, and engine in the original were replaced with corner, stone, book, and stick, which were deemed more culturally appropriate. In the learning phase, the list is read out to the participant, who is immediately asked to recall the words they remember. This process is repeated three times, giving a total learning score out of 30. In the 10/66 protocol, approximately five minutes later, after a series of unrelated CSI 'D' questions (name registration, object naming, object function, repetition) the participant is again asked to recall the 10 words with prompting that they were read from a green card, giving a WLR score out of 10.

X.8.1.4 *Mental health status*

A structured comprehensive clinical mental state interview was administered by all sites, the Geriatric Mental State (GMS), version B3 (Copeland et al., 1986). Responses to this 25-40 minute interview are processed using a standard computer algorithm (AGECAT - Automated Geriatric Examination for Computer Assisted Taxonomy) (Copeland et al., 1986) This algorithm generates symptom scores in nine diagnostic clusters: organic brain syndrome dementia); schizophrenia; mania; neurotic and psychotic depression; and obsessional, hypochondriac, phobic, and anxiety neuroses. Scores of 3–5 denote probable cases, scores of 1 and 2 denote subcases, and those of zero denote absent or negligible relevant symptoms. These stage-one diagnoses are organized into final stage-two diagnoses on the basis of a hierarchy imposed by a structured algorithm. The instrument has few cognitive items and mainly tests domains of orientation and short-term memory.

A subset of 12 GMS items contributed particularly towards the determination of the stage 1 organicity diagnostic confidence level. These comprise tests of cognitive ability (knowledge of date of birth and age; discrepancy between stated dates of birth and age; orientation for day, month, year and address; recall of name of interviewer; name of their country's current and previous political leader) and two judgments made by the interviewer (presence of memory deficit, and problems with memory worse than problems with thinking).

X.8.2 Informant interview

Separate interviews were carried out with the chosen informant in which the following information was collected:

a) Socio-demographic information about the informant was gathered together with their mental health, self-assessed using the 20-item Self-Reporting Questionnaire (SRQ-20)(Mari and Williams, 1985) administered to all informants.

b) A caregiver questionnaire was administered only to informants who were providing significant care and included caregiver perceived strain as measured by the Zarit Burden Interview (Zarit et al., 1980, Zarit et al., 1986).

c) The informant section of the CSI'D' asking about cognitive and functional decline in the participant, was administered to all informants;

d) The 'History and Aetiology Schedule – Dementia Diagnosis and Subtype' (HAS-DDS), which provides information on onset and course of dementia, was administered only when there was evidence from the informant section of the CSI'D' of possible cognitive and/ or functional decline (a score of two or more).

e) The Neuropsychiatric Inventory (NPI-Q) (Kaufer et al., 2000)was completed by all informants to assess behavioural and psychological symptoms in the index participants.

f) Where the participant had communication difficulties as a result of dementia, severe mental illness, deafness or mutism, as much sociodemographic and risk factor information as possible was collected from the informant.

X.8.3 Diagnosis of dementia

The 10/66 diagnostic procedures for dementia have been described in detail in an open access publication (Prince et al., 2003). They were based on criteria specially developed and validated by the 10/66 group to be suitable for low education populations in the developing world and to allow comparisons across countries and cultures. The criteria were operationalized as a computer algorithm, applying clinical principles, based upon the 10/66 cognitive tests, mental status interview and informant report: i) the Community Screening

Instrument for Dementia, (CSI'D') COGSCORE, ii) the CERAD 10 word list learning and animal naming tests, iii) the GMS-AGECAT output (Copeland et al., 1986, Prince, 2004) and iv) the History and Aetiology Schedule-Dementia Diagnosis and Subtype (Dewey and Copeland, 2001). DSM-IV was also operationalized as a computer algorithm and was validated against clinical diagnosis in Cuba (Prince et al., 2008). Dementia subtypes were derived using an algorithm following NINCDS ADRDA criteria(McKhann et al., 1984) for Alzheimer's disease and NINDS-AIREN criteria (Roman et al., 1993) for vascular dementia.

X.9 Statistical Analyses

In the next five chapters several statistical analyses were conducted, in relationship with the objectives' proposed in each of them, they are extensively described in chapters XI to XV. All analyses were carried out using STATA 9.2 (Stata Corp. 2007. Stata Statistical Software: Release 10. College Station, TX: StataCorp LP) on release 1_5 of the 10/66 baseline dataset.

XI. – POPULATION NORMATIVE DATA

The material contained in this chapter is an original transcript of the published paper and therefore repeats some earlier methodological description and does not maintain the same structure of the rest similar chapters of this thesis.

http://www.biomedcentral.com/1471-2377/9/48

Sosa AL, Albanese E, Prince M, Acosta D, Ferri CP, Guerra M, Huang Y, Jacob KS, Rodríguez JL, Salas A, Yang F, Gaona C, Joteeshwaran AT, Rodríguez G, de la Torre GR, Williams JD, Stewart R. Population normative data for the 10/66 Dementia Research Group cognitive test battery from Latin America, India and China: a cross-sectional survey. *BMC Neurology* 2009; 9: 48.

INTRODUCTION

Rapid demographic ageing around the world has important implications for health and social care. Cognitive decline and dementia have a high individual impact and are strongly age-associated (Prince et al., 2000), so that their overall prevalence and societal impact is increasing rapidly. A recent consensus report estimated that the number of people with dementia in the world would increase from 24 million to 82 million from 2000 to 2040 (Ferri et al., 2005). This increase will be particularly marked in low and middle-income countries where epidemiological research into the aetiology and impact of dementia and cognitive decline is limited. The 10/66 Dementia Research Program was set up to facilitate research in these regions and to provide data that can be used for public health and service planning (Prince et al., 2000). Cognitive tests, covering multiple domains are an essential component of a definitive dementia diagnostic assessment, for the purposes of establishing the criterion of decline in at least two domains of cognitive function, including memory (American Psychiatric Association, 1994). Normative data are urgently required, given the influence of both education and culture on cognitive test performance (Berres et al., 2000; Stewart et al., 2002).

The data presented in this paper were drawn from the 10/66 Dementia Research Group's cross-sectional surveys of older people carried out in seven urban and four rural sites in five Latin American countries, China and India. The primary objective was to generate site-specific norms for the cognitive test battery used in the 10/66 studies comprising tests of general cognitive function, verbal fluency and immediate and delayed verbal recall. Further objectives were a) to assess the independent influences of age, educational level and gender

and their homogeneity across sites and b) to assess the extent to which variance attributable to site could be attributed to the effects of region and/ or rural versus urban residence.

METHOD

Study design

The design of the 10/66 Dementia Research Group (DRG) baseline population-based studies has been described in detail (Prince et al., 2007). Briefly, cross-sectional surveys were carried out; approaching all residents aged 65 and over within purposively selected geographically defined catchment areas at each site. Affluent districts were intentionally avoided. A target sample of 2000 persons aged 65 years and over, per country (3,000 in Cuba) was identified by means of door knocking the catchment areas. Peru, Mexico, China and India recruited both from rural and urban sites. Interviews followed a comprehensive one-phase design where all participants received a full assessment, including: cognitive and mental health evaluation, an informant interview, a physical and neurological examination, blood assays and genotyping, in addition to questionnaire measures of environmental and behavioural risk exposures, sociodemographic and socioeconomic status, and physical health status. Disability, health service utilisation, care arrangements and impact of providing care were also evaluated.

Measurements

For this analysis we considered the following socio-demographic independent variables: participants' age divided into four groups (65-69 years, 70-74 years, 75-79 years, 80 years

and over), sex, and education level divided into five groups (none, some (but did not complete primary), completed primary, completed secondary, and tertiary).

The 10/66 cognitive assessment battery was drawn principally from the Community Screening Instrument for Dementia (CSI'D') developed by the Ibadan-Indianapolis study group (Hall et al., 1993) specifically for use in cross-cultural research, and in low education settings, and from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD; Morris et al., 1989). As such, components of the battery have been very widely used in other population and clinical research. In our large multi-site pilot study (Prince et al., 2003) we developed and validated a culture and education-fair algorithm for dementia diagnosis across a wide variety of low and middle income country settings, comprising components of the cognitive test battery, in combination with the Geriatric Mental State and the informant section of the CSI'D'

The analysis described here focussed on the four main tests included in the 10/66 cognitive test battery:

1) Global cognitive function: The Community Screening Instrument for Dementia (CSI 'D'; Hall et al., 1993) includes a 32 item culture and education-fair cognitive test assessing orientation, comprehension, memory, naming and language expression, which is used to generate a total cognitive score (COGSCORE). The CSI'D' has been used across cultures with the minimum of necessary adaptation. It was developed and first validated among Cree American Indians (Hall et al., 1993; Hendrie et al., 1993), further validated and used in population-based research (The NIA US-Nigeria Study) among Nigerians in Ibadan and

African-Americans in Indianapolis (Hendrie et al., 1995), and has also been validated among white Canadians in Winnipeg (Hall et al., 2000), and in Jamaica (Unverzagt et al., 1999). The CSI'D' test score distributions among those with dementia and controls, and the degree of discrimination provided were remarkably consistent across these five very different cultural settings (Hall et al., 2000).

2) Memory: The 10/66 battery includes two elements of the CERAD 10 word list learning test; world list memory (WLM) and word list recall (WLR); testing short term memory, registration and recall. WLR has been reported to be of particular value in distinguishing early dementia from normal aging (Welsh et al., 1991). WLM and WLR are taken from the adapted CERAD ten word list-learning task used in the Indo-US Ballabgarh dementia study (Ganguli et al., 1996). Six words; butter, arm, letter, queen, ticket, and grass; were taken from the original CERAD battery English language list (Guruje et al., 1995). Pole, shore, cabin, and engine were replaced with corner, stone, book and stick, which were deemed more culturally appropriate. In the learning phase, the list is read out to the participant from a green card, who is then asked to recall straight away the words that they remember. This process is repeated three times, giving a WLM score out of 30. Five minutes later the participant is again asked to recall the 10 words with prompting that they were read from a green card, giving a WLR score out of 10.

3) Verbal fluency (VF): the animal naming verbal fluency task from the CERAD is administered as part of the CSI 'D', however it is accorded very little weight within the algorithm for calculating the total CSI 'D' score. In the version of the test used in CSI 'D', after a brief practice naming items from another category (clothing), participants are encouraged to name as many different animals as they can in the space of one minute. The instructions read out to the participant stipulate: 'think of any kinds of animal in the air, on

land, in the water, in the forest, all the different animals'. If the participant stops before the allotted time has elapsed they are encouraged to continue. The score is one point for each valid name. In the computation of the CSI 'D' cognitive test (COGSCORE) the VF score is divided by 23; weighted scores generally range between 0 and 1, the same as for a single CSI 'D' orientation item.

VF, WLM and WLR are taken with minimal adaptation from the battery of cognitive tests proposed by the Consortium to Establish a Registry for Alzheimer's disease (CERAD). The CERAD neuropsychological battery has been adapted for use in India (Ganguli et al., 1996), Korea (Lee et al., 2004), Brazil (Bertolucci et al., 2001), Nigeria (Guruje et al., 1995) and Jamaica (Unverzagt et al., 1999), and norms have been provided for black and white persons in the USA, both with dementia (Welsh et al., 1995), and among the general population (Fillenbaum et al., 2001). While education effects are prominent, cultural or ethnic differences have been less evident, CERAD battery components each distinguish reliably between those with dementia and controls across cultures (Ganguli et al., 1996; Unverzagt et al., 1999).

Statistical analysis

For this analysis, all participants who had received a diagnosis of dementia according to either DSM-IV or 10/66 dementia criteria were excluded. Participants' age, sex and education data were described by site. Means and standard deviations (SD) for each of the four cognitive tests were calculated by age, sex and education for each of the eleven sites. General linear models were used to determine the unadjusted and independent effects of

age, sex and education on cognitive test scores across sites. We then tested formally for effect modification by extending the models used to estimate the main effects of age, education and sex to include site by age, site by education and site by sex interaction terms. Finally, we estimated the proportion of the variance (eta^2) in each cognitive test accounted for by age, education, gender and site. We further sought to disaggregate the variance accounted for by site by substituting this variable with two further variables sub-classifying sites into region (Latin America versus China, versus India) and rural or urban location. The effect of region (controlling for age, education, gender and rural/ urban location) is summarised as adjusted means and mean differences with 95% confidence intervals for the two contrasts; China versus Latin America and India versus Latin America. All analyses were carried out using STATA 9.2 (StataCorp. 2007. *Stata Statistical Software: Release* 10. College Station, TX: StataCorp LP) on release 1_5 of the 10/66 baseline dataset.

RESULTS.

Response rates across all countries ranged between 72% and 98%. In all 14,967 participants were fully evaluated. One thousand three hundred and eighteen of these met criteria for dementia and were excluded from further analysis, leaving a total of 13,649 participants, free of dementia (Table 1).

Table 1 Sociodemographic characteristics of participants by site

Region	**Latin America**							**China**		**India**	
Country	**Cuba**	**DR**	**Peru**		**Venezuela**	**Mexico**		**China**		**India**	
Rural or urban site	Urban	Urban	Urban	Rural	Urban	Urban	Rural	Urban	Rural	Urban	Rural
Total (n)	2,621	1,769	1,251	516	1,826	910	913	1,076	946	930	891
Age in years (MV)	7	0	1	0	23	1	0	0	0	4	0
65 – 69 years %	28.2	29.0	29.2	33.5	44.1	26.7	32.2	28.7	39.9	42.9	34.8
70 – 74 years %	28.3	27.3	27.3	25.8	24.9	34.4	26.2	32.5	30.1	32.1	34.9
75 – 79 years %	22.3	19.5	21.9	18.2	17.8	20.2	22.1	21.9	19.3	14.6	17.7
80+ years %	21.3	24.3	21.6	22.5	13.1	18.7	19.5	16.8	11.0	10.5	12.6
Females (MV)	0	2	0	0	60	0	0	0	0	15	0
%	64.4	65.4	64.1	52.5	63.5	65.6	59.9	56.6	55.3	57.3	52.3
Education (MV)	8	19	8	8	63	0	0	0	0	2	0
No education. %	2.1	17.8	2.5	14.0	7.3	19.6	31.0	19.2	57.2	41.3	63.6
Some education (did not complete primary) %	20.9	51.8	6.4	25.6	22.1	35.7	52.3	12.8	11.5	24.2	21.0
Completed primary %	33.0	19.1	31.8	49.6	49.4	24.2	12.8	26.5	26.3	20.8	12.4
Completed secondary %	26.0	7.1	36.1	6.6	14.3	10.4	2.4	29.4	4.4	9.1	2.8
Completed tertiary %	17.9	3.7	22.8	3.1	5.0	10.1	1.5	12.1	0.5	4.4	0.2

DR = Dominican Republic; MV= Missing Value

All age groups were well represented. The Venezuelan, rural Chinese and Indian samples had a younger age distribution than other sites. The female/ male ratio exceeded 1 in all sites, but with a less striking preponderance of women in rural Peru, China and India.

Educational level showed considerable variation across sites, highest in urban Latin America sites (other than the Dominican Republic), and lowest in rural China and in India. Within country, educational levels were consistently higher in urban compared with rural sites.

Tables 2 to 5 present normative data; stratified means and standard deviations for the four cognitive outcomes. Older age and lower levels of education were consistently associated with poorer cognitive test performance on scores for all four tests, across all sites. The effect of sex on cognitive test performance was smaller and more variable, both between tests and between sites. Men tended to perform marginally better than women on the COGSCORE, and on VF. For WLM and WLR, women performed better than men in Latin American sites, but there was no gender difference in China and India.

Tests for interaction indicated that the effects of age, sex and education on cognitive test performance were each significantly modified by site, for all four cognitive tests. However, the effects were uniformly very modest in size, generally accounting for between 0.1% and 0.3% of the overall variance. The two largest interaction effects were those between site and age (0.6% of the variance) and site and education (0.5%) for verbal fluency.

Table 2 Mean (SD) scores for global cognitive function (CSI'D' 'COGSCORE') by demographic status and site

	Country										
	Cuba	DR	Peru		Venezuela	Mexico		China		India	
	Urban	Urban	Urban	Rural	Urban	Urban	Rural	Urban	Rural	Urban	Rural
Age											
65 - 69	31.1 (1.9)	30.4 (2.3)	31.8 (1.3)	30.6 (2.9)	31.1 (1.8)	30.8 (1.7)	29.8 (2.1)	31.7 (1.2)	31.0 (3.9)	29.2 (3.0)	27.9 (3.2)
70 - 74	30.8 (1.9)	30.2 (2.1)	31.3 (2.2)	30.4 (1.8)	30.6 (2.2)	30.1 (2.8)	29.3 (1.9)	31.4 (2.0)	30.7 (2.6)	28.3 (3.7)	27.3 (4.3)
75 - 79	30.3 (2.1)	29.9 (2.1)	31.1 (2.4)	29.7 (2.7)	30.1 (2.5)	29.5 (2.8)	28.5 (3.4)	31.4 (1.5)	29.6 (4.3)	28.5 (4.0)	27.0 (3.6)
80+	29.5 (2.6)	28.7 (2.8)	29.6 (3.4)	28.9 (3.4)	29.0 (2.8)	29.3 (2.4)	28.3 (2.6)	30.9 (2.8)	29.1 (3.7)	27.6 (3.4)	25.3 (7.3)
Crude β (95%	-0.5	-0.5	-0.6	-0.6	-0.6	-0.5	-0.5	-0.2	-0.7	-0.8	-0.8
C.I.)	(-0.6 to -0.5)	(-0.6 to -0.4)	(-0.8 to -0.5)	(-0.8 to -0.4)	(-0.7 to-0.5)	(-0.7 to -0.4)	(-0.7 to -0.4)	(-0.3 to -0.1)	(-0.9 to -0.4)	(-0.7 to -0.3)	(-1.0 to -0.5)
Adj. β[1]	-0.4	-0.5	-0.6	-0.5	-0.5	-0.4	-0.5	-0.2	-0.6	-0.5	-0.8
(95% C.I.)	(-0.4 to -0.3)	(-0.6 to -0.4)	(-0.7 to -0.4)	(-0.7 to -0.3)	(-0.6 to -0.4)	(-0.5 to -0.2)	(-0.6 to -0.3)	(-0.3 to -0.9)	(-0.8 to -0.3)	(-0.7 to -0.3)	(-1.1 to -0.5)
Sex											
Females	30.4 (2.3)	29.6 (2.6)	31.0 (2.2)	29.9 (2.7)	30.4 (1.89)	29.9 (2.5)	29.0 (2.5)	31.2 (2.3)	30.2 (3.1)	27.9 (3.4)	26.0 (5.3)
Males	30.7 (2.1)	30.2 (2.01)	31.1 (2.9)	30.2 (3.0)	30.7 (2.54)	30.2 (2.5)	29.2 (2.7)	31.6 (1.2)	30.7 (4.3)	29.7 (3.1)	28.5 (2.52)
Crude β	0.3	0.6	0.0	0.3	0.3	0.4	0.2	0.4	0.5	1.9	2.6
(95% C.I.)	(0.1 to 0.5)	(0.3 to 0.8)	(-0.2 to 0.3)	(-0.2 to 0.7)	(0.1 to 0.5)	(0.0 to 0.7)	(-0.1 to 0.5)	(0.2 to 0.7)	(0.0 to 0.9)	(1.4 to 2.3)	(2.0 to 3.1)
Adj. β[2]	0.1	0.4	0.0	0.1	0.2	0.4	0.2	0.2	0.1	1.0	1.4
(95% C.I.)	(-0.1 to 0.2)	(0.1 to 0.6)	(-0.2 to 0.3)	(-0.4 to 0.6)	(-0.0 to 0.4)	(0.0 to 0.7)	(-0.1 to 0.6)	(-0.1 to 0.4)	(-0.5 to 0.6)	(0.6 to 1.4)	(0.8 to 2.1)
Education											
No Ed.	28.3 (3.7)	28.2 (3.1)	28.7 (3.1)	27.9 (3.7)	29.1 (1.9)	28.5 (2.7)	27.8 (3.3)	30.6 (2.7)	30.1 (3.5)	27.0 (3.3)	26.1 (5.0)
Some Ed.	29.3 (2.5)	29.8 (2.2)	29.8 (2.6)	29.9 (2.2)	29.7 (2.3)	29.5 (2.9)	29.4 (2.1)	30.7 (1.4)	30.3 (3.5)	29.0 (3.3)	28.5 (1.9)
Primary	30.4 (1.8)	30.8 (1.6)	30.6 (2.4)	30.6 (1.9)	30.8 (1.6)	30.6 (1.7)	30.3 (1.8)	31.5 (2.1)	31.0 (4.2)	29.8 (3.5)	30.0 (1.6)
Secondary	31.1 (1.5)	31.1 (1.7)	31.3 (2.7)	30.1 (5.6)	31.1 (3.2)	31.3 (1.3)	30.7 (1.6)	31.9 (1.1)	32.0 (0.7)	31.1 (1.2)	30.9 (1.3)
Tertiary	31.7 (2.2)	31.1 (1.7)	31.7 (1.4)	31.1 (0.9)	31.3 (1.5)	31.6 (1.2)	31.5 (1.2)	32.0 (0.9)	31.4 (1.8)	31.0 (1.5)	31.4 (1.7)
Crude β (95%	0.8	0.7	0.6	0.6	0.4	0.7	0.8	0.3	0.3	0.9	1.2
C.I.)	(0.7 to 0.8)	(0.6 to 0.8)	(0.5 to 0.7)	(0.4 to 0.8)	(0.3 to 0.5)	(0.6 to 0.8)	(0.7 to 0.9)	(0.2 to 0.4)	(0.2 to 0.5)	(0.8 to 1.0)	(1.0 to 1.5)
Adj. β [3]	0.7	0.6	0.5	0.6	0.5	0.6	0.7	0.3	0.2	0.8	0.9
(95% C.I.)	(0.6 to 0.7)	(0.5 to 0.7)	(0.3 to 0.6)	(0.4 to 0.7)	(0.4 to 0.6)	(0.5 to 0.7)	(0.6 to 0.9)	(0.2 to 0.4)	(0.1 to 0.4)	(0.7 to 0.9)	(0.7 to 1.2)

DR = Dominican Republic

1. Adjusted for sex and education
2. Adjusted for age and education
3. Adjusted for age and sex

Table 3 Mean (SD) scores for CERAD verbal fluency (animal naming) test by demographic status and site

	Country										
	Cuba	DR	Peru		Venezuela	Mexico		China		India	
	Urban	Urban	Urban	Rural	Urban	Urban	Rural	Urban	Rural	Urban	Rural
Age											
65 - 69	18.1 (6.2)	15.0 (4.8)	19.3 (5.5)	17.1 (4.9)	20.1 (6.3)	16.9 (5.1)	14.9 (4.2)	17.3 (4.6)	16.2 (5.7)	8.9 (3.3)	10.4 (3.6)
70 - 74	16.9 (5.8)	14.2 (4.9)	18.2 (5.3)	16.1 (5.1)	18.0 (6.0)	15.7 (5.1)	14.1 (4.4)	16.8 (4.7)	15.8 (5.1)	8.6 (3.4)	10.1 (3.8)
75 - 79	15.9 (5.4)	13.7 (4.3)	16.9 (4.8)	15.2 (3.7)	16.8 (5.7)	15.2 (4.8)	13.0 (4.5)	16.3 (4.5)	14.1 (5.2)	8.4 (3.3)	9.5 (3.3)
80+	14.7 (5.6)	12.3 (4.4)	14.3 (5.1)	14.4 (5.0)	14.8 (5.8)	14.3 (5.1)	13.0 (4.6)	15.8 (4.8)	13.1 (5.0)	7.4 (2.5)	9.1 (4.4)
Crude **β** (95% C.I.)	-1.1 (-1.3 to -0.9)	-0.9 (-1.1 to -0.7)	-1.6 (-1.9 to -1.3)	-0.9 (-1.3 to -0.5)	-1.7 (-2.0 to -1.4)	-0.8 (-1.1 to -0.5)	-0.7 (-1.0 to -0.5)	-0.5 (-0.8 to -0.3)	-1.0 (-1.4 to -0.7)	-0.4 (-0.6 to -0.2)	-0.4 (-0.7 to -0.2)
Adj. **β**[1] (95% C.I.)	-0.7 (-0.9 to -0.5)	-0.8 (-1.0-0.6)	-1.4 (-1.7 to -1.2)	-0.8 (-1.2 to -0.5)	-1.4 (-1.7 to -1.1)	-0.6 (-0.9 to -0.2)	-0.7 (-0.9 to -0.4)	-0.5 (-0.8 to -0.3)	-0.7 (-1.1 to -0.4)	-0.4 (-0.6 to -0.1)	-0.4 (-0.6 to -0.2)
Sex											
Females	15.9 (5.6)	13.5 (4.5)	17.2 (5.3)	15.6 (4.7)	18.1 (6.2)	15.5 (5.1)	13.5 (4.3)	16.1 (4.6)	14.8 (5.1)	8.1 (3.1)	9.3 (3.7)
Males	17.7 (6.3)	14.6 (5.1)	17.8 (5.9)	16.2 (5.0)	18.7 (6.6)	16.1 (5.2)	14.4 (4.7)	17.4 (4.6)	15.9 (5.9)	9.4 (3.5)	10.7 (3.6)
Crude **β** (95% C.I.)	1.8 (1.4 to 2.3)	1.1 (0.6 to 1.6)	0.5 (-0.1 to 1.2)	0.6 (-0.2 to 1.4)	0.6 (0.0 to 1.2)	0.6 (-0.1 to 1.3)	0.9 (0.3 to 1.5)	1.2 (0.7 to 1.8)	1.1 (0.4 to 1.8)	1.3 (0.9 to 1.8)	1.4 (1.0 to 1.9)
Adj. **β**[2] (95% C.I.)	1.3 (0.9 to 1.7)	0.9 (0.4 to 1.3)	0.5 (-0.1 to 1.1)	0.5 (-0.3 to 1.3)	0.2 (-0.4 to 0.8)	0.6 (-0.1 to 1.2)	0.9 (0.4 to 1.5)	0.8 (0.3 to 1.4)	-0.1 (-0.8 to 0.7)	0.9 (0.4 to 1.3)	0.9 (0.4 to 1.3)
Education											
No Ed.	13.6 (4.5)	12.8 (4.3)	14.3 (4.5)	13.4 (4.1)	14.8 (5.0)	14.0 (4.4)	12.6 (4.0)	15.3 (4.4)	14.3 (5.1)	7.7 (3.1)	9.3 (3.6)
Some Ed.	13.9 (5.0)	13.4 (4.4)	14.7 (4.6)	15.7 (5.0)	16.7 (6.6)	14.5 (4.7)	14.1 (4.5)	15.2 (5.1)	14.3 (5.1)	8.9 (3.4)	10.3 (3.3)
Primary	15.6 (5.28)	14.8 (5.0)	16.1 (4.9)	16.5 (4.5)	18.8 (6.1)	16.2 (4.9)	14.8 (4.2)	17.1 (4.4)	17.5 (5.7)	10.0 (3.0)	12.0 (3.2)
Secondary	17.2 (5.5)	15.8 (5.2)	17.7 (5.6)	16.9 (6.3)	19.7 (6.0)	18.1 (4.3)	18.0 (4.5)	17.6 (4.2)	17.6 (6.4)	10.3 (3.5)	14.0 (4.1)
Tertiary	20.7 (6.4)	16.8 (5.7)	19.7 (5.7)	16.1 (6.2)	21.7 (7.3)	19.4 (6.0)	18.3 (5.0)	17.2 (5.2)	17.6 (2.7)	9.7 (3.03)	16.0 (2.8)
Crude **β** (95% C.I.)	1.9 (1.7 to 2.1)	0.7 (0.6 to 0.9)	1.4 (1.2 to 1.7)	0.8 (0.4 to 1.1)	1.2 (0.9 to 1.4)	1.1 (0.9 to 1.3)	0.9 (0.7 to 1.1)	0.5 (0.4 to 0.7)	0.9 (0.7 to 1.1)	0.5 (0.4 to 0.6)	0.9 (0.7 to 1.1)
Adj. **β** [3] (95% C.I.)	1.6 (1.4 to 1.8)	0.6 (0.4 to 0.8)	1.1 (0.8 to 1.4)	0.6 (0.3 to 0.9)	1.3 (1.1 to 1.6)	1.0 (0.8 to 1.2)	0.8 (0.6 to 1.1)	0.4 (0.2 to 0.6)	0.7 (0.5 to 1.0)	0.4 (0.3 to 0.6)	0.8 (0.5 to 1.0)

DR = Dominican Republic

1. Adjusted for sex and education
2. Adjusted for age and education
3. Adjusted for age and sex

Table 4 Mean (SD) scores for CERAD word list memory test by demographic status and site

	Country										
	Cuba	**DR**	**Peru**		**Venezuela**	**Mexico**		**China**		**India**	
	Urban	Urban	Urban	Rural	Urban	Urban	Rural	Urban	Rural	Urban	Rural
Age											
65 - 69	17.0 (3.9)	15.07 (3.65)	16.9 (3.8)	14.0 (3.8)	16.3 (4.0)	15.0 (3.6)	13.7 (3.6)	18.7 (4.2)	15.5 (4.3)	13.5 (4.8)	8.9 (3.9)
70 - 74	16.0 (4.1)	14.37 (3.78)	15.7 (3.5)	13.2 (3.7)	15.0 (3.9)	13.5 (4.0)	12.4 (3.9)	18.0 (4.0)	14.6 (3.6)	12.3 (4.5)	7.9 (3.7)
75 - 79	15.1 (3.8)	13.43 (3.52)	14.4 (3.9)	11.9 (3.9)	14.3 (4.3)	12.1 (3.7)	11.3 (4.0)	17.5 (4.4)	13.0 (4.2)	11.6 (4.6)	8.0 (3.9)
80+	14.0 (4.1)	12.24 (3.84)	12.6 (3.6)	11.6 (3.9)	13.0 (3.9)	11.7 (4.1)	11.2 (3.8)	16.4 (4.7)	12.6 (3.6)	10.8 (4.1)	5.9 (4.2)
Crude **β** (95% C.I.)	-1.0 (-1.1 to -0.8)	-0.9 (-1.1 to -0.8)	-1.4 (-1.6 to -1.2)	-0.8 (-1.1 to -0.5)	-1.1 (-1.2 to -0.9)	-1.1 (-1.4 to -0.9)	-0.9 (-1.1 to -0.7)	-0.7 (-1.0 to -0.5)	-1.1 (-1.3 to -0.8)	-0.9 (-1.2 to -0.6)	-0.8 (-1.1 to -0.5)
Adj. **β**[1] (95% C.I.)	-0.7 (-0.8 to -0.6)	-0.9 (-1.0 to -0.7)	-1.2 (-1.4 to -1.0)	-0.7 (-0.9 to -0.4)	-0.9 (-1.1 to -0.7)	-0.9 (-1.1 to -0.6)	-0.7 (-1.0 to -0.5)	-0.7 (-0.9 to -0.4)	-0.9 (-1.2 to -0.6)	-0.9 (-1.2 to -0.6)	-0.7 (-1.0 to -0.5)
Sex											
Females	15.6 (4.2)	14.1 (3.8)	15.4 (4.0)	13.4 (4.1)	15.4 (4.2)	13.7 (3.9)	12.9 (3.9)	17.5 (4.1)	14.1 (3.8)	12.2 (4.5)	7.5 (4.1)
Males	15.5 (4.0)	13.5 (3.9)	14.5 (4.0)	12.3 (3.72)	14.9 (4.1)	12.5 (4.3)	11.5 (3.9)	18.3 (4.5)	14.8 (4.5)	13.0 (4.9)	8.5 (3.7)
Crude **β**	-0.1	-0.6	-1.0	-1.1	-0.5	-1.2	-1.3	0.8	0.8	0.8	1.0
(95% C.I.)	(-0.4 to 0.2)	(-1.0 to -0.2)	(-1.4 to -0.5)	(-1.8 to -0.5)	(-0.9 to -0.1)	(-1.7 to -0.6)	(-1.8 to -0.8)	(0.3 to 1.3)	(0.2 to 1.3)	(0.1 to 1.4)	(0.5 to 1.5)
Adj. **β**[2]	-0.4	-0.8	-1.0	-1.4	-0.8	-1.1	-1.2	0.1	0.1	-0.3	-0.1
(95% C.I.)	(-0.7 to -0.1)	(-1.2 to -0.5)	(-1.4 to -0.5)	(-2.0 to -0.7)	(-1.2 to -0.4)	(-1.6 to -0.6)	(-1.7 to -0.7)	(-0.4 to 0.7)	(-0.5 to 0.7)	(-0.9 to 0.3)	(-0.7 to 0.5)
Education											
No Ed.	13.4 (4.9)	13.0 (3.8)	12.3 (4.7)	10.6 (3.49)	12.1 (4.0)	11.7 (3.8)	11.3 (3.6)	16.3 (4.0)	13.8 (3.9)	11.0 (4.3)	7.2 (3.8)
Some Ed.	13.9 (4.0)	13.5 (3.7)	13.1 (3.7)	12.8 (3.91)	14.5 (4.3)	12.2 (3.8)	12.5 (3.9)	16.1 (3.7)	14.1 (4.1)	12.2 (4.1)	8.8 (3.5)
Primary	15.2 (3.9)	14.7 (3.6)	14.3 (3.9)	13.4 (3.76)	15.6 (3.9)	13.9 (3.7)	13.1 (3.7)	17.7 (4.2)	15.4 (4.3)	14.0 (4.3)	10.1 (4.1)
Secondary	16.2 (3.9)	15.7 (4.1)	15.4 (3.9)	13.5 (4.65)	15.9 (4.0)	15.1 (3.6)	14.9 (3.7)	18.9 (4.1)	17.0 (4.7)	16.0 (5.2)	10.8 (3.9)
Tertiary	17.8 (3.9)	16.1 (4.5)	16.6 (4.0)	15.1 (4.5)	16.7 (4.1)	16.8 (3.5)	17.1 (4.9)	19.7 (4.7)	14.8 (6.5)	15.5 (4.8)	12.5 (3.5)
Crude **β**	1.1	0.6	1.0	0.8	0.8	1.0	0.7	0.7	0.6	1.0	0.9
(95% C.I.)	(1.0 to 1.3)	(0.5 to 0.8)	(0.8 to 1.2)	(0.5 to 1.0)	(0.6 to 0.9)	(0.8 to 1.1)	(0.5 to 0.9)	(0.5 to 0.9)	(0.4 to 0.7)	0.8 to 1.2)	(0.7 to 1.1)
Adj. **β** [3]	1.0	0.6	0.8	0.8	0.9	0.9	0.7	0.7	0.4	1.0	0.9
(95% C.I.)	(0.8 to 1.1)	(0.4 to 0.7)	(0.6 to 1.0)	(0.5 to 1.0)	(0.7 to 1.1)	(0.7 to 1.1)	(0.5 to 0.9)	(0.5 to 0.8)	(0.2 to 0.6)	(0.8 to 1.2)	(0.7 to 1.1)

DR = Dominican Republic

1. Adjusted for sex and education
2. Adjusted for age and education
3. Adjusted for age and sex

Table 5 Mean (SD) scores for CERAD word list recall test by demographic status and site

	Country										
	Cuba	**DR**	**Peru**		**Venezuela**	**Mexico**		**China**		**India**	
	Urban	Urban	Urban	Rural	Urban	Urban	Rural	Urban	Rural	Urban	Rural
Age											
65 - 69	5.7 (1.9)	4.8 (1.9)	5.7 (1.8)	4.8 (1.9)	5.6 (2.0)	5.1 (1.7)	4.8 (1.8)	7.0 (1.6)	4.2 (1.75)	4.63 (1.96)	3.2 (1.8)
70 - 74	5.3 (1.8)	4.4 (1.8)	5.2 (1.8)	4.5 (1.9)	5.2 (2.0)	4.6 (1.8)	4.1 (1.9)	6.8 (1.7)	3.9 (1.67)	4.19 (1.97)	2.9 (1.7)
75 - 79	4.9 (1.9)	4.1 (1.8)	4.6 (1.8)	3.6 (1.8)	4.8 (2.1)	4.0 (1.8)	3.6 (2.0)	6.5 (1.9)	3.3 (1.72)	3.87 (2.17)	2.8 (1.7)
80+	4.3 (1.8)	3.5 (1.9)	3.8 (1.9)	3.5 (2.0)	4.1 (2.0)	3.6 (1.8)	3.7 (1.9)	6.1 (2.2)	3.3 (1.63)	3.31 (2.13)	2.1 (1.6)
Crude **β**	-0.4	-0.4	-0.6	-0.5	-0.5	-0.5	-0.4	-0.3	-0.4	-0.4	-0.3
(95% C.I.)	(-0.5 to -0.4)	(-0.5 to -0.4)	(-0.7 to -0.5)	(-0.6 to -0.3)	(-0.6 to -0.4)	(-0.6 to -0.4)	(-0.5 to -0.3)	(-0.4 to -0.2)	(-0.5 to -0.3)	(-0.6 to -0.3)	(-0.4 to -0.2)
Adj. **β**[1]	-0.3	-0.4	-0.6	-0.4	-0.4	-0.4	-0.3	-0.3	-0.3	-0.4	-0.3
(95% C.I.)	(-0.4 to -0.3)	(-0.5 to -0.3)	(-0.6 to -0.5)	(-0.5 to -0.3)	(-0.5 to -0.3)	(-0.5 to -0.3)	(-0.5 to -0.2)	(-0.4 to -0.2)	(-0.4 to -0.2)	(-0.6 to -0.3)	(-0.4 to -0.2)
Sex											
Females	5.1 (1.9)	4.4 (1.9)	5.1 (2.0)	4.4 (2.1)	5.3 (2.0)	4.6 (1.9)	4.3 (2.0)	6.6 (1.8)	3.7 (1.7)	4.2 (1.94)	2.7 (1.7)
Males	5.0 (1.9)	4.0 (1.8)	4.6 (1.9)	3.9 (1.9)	4.9 (2.0)	4.1 (1.9)	3.8 (1.9)	6.8 (1.9)	4.0 (1.8)	4.3 (2.2)	3.1 (1.8)
Crude **β**	-0.1	-0.3	-0.5	-0.5	-0.3	-0.5	-0.5	0.3	0.2	0.2	0.4
(95% C.I.)	(-0.3 to 0.0)	(-0.5 to -0.2)	(-0.7 to -0.2)	(-0.8 to -0.2)	(-0.5 to -0.1)	(-0.8 to -0.3)	(-0.8 to -0.3)	(0.1 to 0.5)	(0.0 to 0.5)	(-0.1 to 0.4)	(0.2 to 0.6)
Adj. **β**[2]	-0.2	-0.4	-0.4	-0.6	-0.4	-0.5	-0.5	0.0	0.0	-0.2	0.0
(95% C.I.)	(-0.4 to -0.1)	(-0.6 to -0.3)	(-0.7 to -0.2)	(-0.9 to -0.3)	(-0.6 to -0.2)	(-0.7 to -0.21)	(-0.7 to -0.2)	(-0.2 to 0.3)	(-0.3 to 0.2)	(-0.5 to 0.04)	(-0.3 to 0.2)
Education											
No Ed.	4.2 (2.1)	4.0 (2.0)	4.0 (2.0)	3.1 (1.8)	4.1 (1.7)	3.9 (1.9)	3.7 (2.1)	6.2 (1.9)	3.6 (1.7)	3.7 (2.0)	2.6 (1.6)
Some Ed.	4.4 (1.9)	4.1 (1.8)	4.3 (1.9)	4.1 (2.2)	4.9 (2.1)	4.0 (1.8)	4.2 (1.9)	5.7 (1.8)	4.0 (1.7)	3.9 (1.8)	3.2 (1.8)
Primary	5.0 (1.8)	4.5 (1.7)	4.5 (1.9)	4.4 (1.8)	5.3 (2.0)	4.7 (1.8)	4.5 (1.8)	6.8 (1.7)	4.2 (1.8)	4.8 (2.0)	3.7 (1.8)
Secondary	5.3 (1.8)	4.9 (1.9)	5.1 (1.8)	4.8 (1.7)	5.3 (1.9)	5.3 (1.9)	5.1 (2.2)	7.1 (1.7)	4.6 (1.9)	5.5(2.1)	4.1 (1.7)
Tertiary	6.0 (2.0)	5.0 (2.1)	5.4 (2.0)	5.4 (1.7)	5.8 (2.1)	5.4 (1.7)	5.8 (1.6)	7.3 (1.9)	3.8 (2.7)	5.3 (1.6	4.0 (1.4)
Crude **β**	0.5	0.2	0.4	0.4	0.3	0.3	0.3	0.3	0.2	0.3	0.3
(95% C.I.)	(0.4 to 0.5)	(0.1 to 0.3)	(0.3 to 0.5)	(0.2 to 0.5)	(0.2 to 0.4)	(0.3 to 0.4)	(0.2 to 0.4)	(0.2 to 0.3)	(0.1 to 0.3)	(0.3 to 4.0)	(0.2 to 0.4)
Adj. **β**[3]	0.4	0.2	0.3	0.4	0.3	0.3	0.3	0.2	0.2	0.4	0.3
(95% C.I.)	(0.3 to 0.5)	(0.1 to 0.3)	(0.2 to 0.4)	(0.2 to 0.5)	(0.2 to 0.4)	(0.2 to 0.4)	(0.2 to 0.4)	(0.2 to 0.3)	(0.1 to 0.2)	(0.3 to 0.4)	(0.2 to 0.4)

DR = Dominican Republic

1. Adjusted for sex and education
2. Adjusted for age and education
3. Adjusted for age and sex

Table 6, summarises the independent effects of age, sex, education and site on cognitive test performance. Site accounted for the highest proportion of variance for all four scores followed by education and then age, apart from WLR where the effect of age was stronger than education. The contribution of sex to the models was uniformly low. Most of the effect of site could be more parsimoniously accounted for by region (Latin America versus China versus India), and, to a lesser extent, rural versus urban location, with marginally poorer performance on WLM and WLR in rural compared with urban settings. Controlling for age, education, sex and rural/ urban location, performance on all cognitive tests was best among Chinese participants, intermediate among Latin American participants, and worst among Indian participants. Chinese participants scored one point more and

Indian participants one and a half point less on the COGSCORE than did participants in Latin American sites. Indian participants generated nearly six fewer animals on verbal fluency than did participants in China and Latin America. Compared with Latin American participants Chinese participants remembered nearly three more words out of 30 on WLM and one more word out of 10 on delayed WLR; Indian participants recalled two and a half words fewer on WLM and half a word fewer on WLR.

Table 6 The independent effects of age, education, sex and site on the four cognitive assessments, further decomposing the effect of site into region and rural/ urban location

	The independent, mutually adjusted effects (eta² %) of age, education, sex and site on cognitive test performance				Unpacking 'site' – th independent effects (eta² %) of region ar rural/ urban locatior		The effect of region, adjusting for age, education, sex and rural/ urban location			
Cognitive te	Age	Education	Sex	Site	Region	Rural/ Urban	Parameter	Latin Americ	China	India
CSI'D' COGSCORI	3.3%	7.0%	0.4%	7.6%	6.8%	0.5%	Adjusted mean	30.0 (29.9-30.1)	31.1 (31.0-31.2)	28.5 (28.3-28.6)
							Mean difference	Reference	1.1 (0.9 to1.2)	-1.6 (-1.7 to -1.4)
Verbal Fluency	3.1%	5.1%	0.4%	15.8%	12.2%	0.0%	Adjusted mean	16.0 (15.9-16.1)	16.3 (16.1-16.5)	10.2 (10.0-10.5)
							Mean difference	Reference	0.3 (0.0 to 0.5)	-5.8 (-6.1 to -5.5)
Word list memory	4.9%	6.5%	0.5%	16.0%	11.6%	4.1%	Adjusted mean	13.5 (13.4-13.6)	16.3 (16.1-16.5)	16.0 (10.7-11.2)
							Mean difference	Reference	2.8 (2.6 to 3.0)	-2.5 (-2.8 to -2.3)
Word list recall	4.7%	4.0%	0.6%	11.6%	5.1%	3.5%	Adjusted mean	4.3 (4.3-4.3)	5.4 (5.3-5.5)	3.8 (3.7-3.9)
							Mean difference	Reference	1.1 (1.0 to 1.2)	-0.5 (-0.6 to -0.4)

DISCUSSION

We have provided normative data by age group, sex and educational level for widely used neuropsychological tests of global cognitive function, verbal fluency and immediate and delayed recall for seven LAMICs. Those with all degrees of dementia, including questionable dementia were excluded. These norms have been rigorously generated applying a standardized testing procedure amongst representative community dwelling samples. To our knowledge this is the largest study to date on neuropsychological tests norms and the first to present direct comparisons between so many culturally diverse countries.

With the exception of rural India, our norms for CERAD WLM and WLR are well aligned with those previously reported from affluent western countries (Welsh et al., 1994; Stewart et al., 2001; Collie et al., 1999). Our norms for CERAD VF are comparable to previously determined norms from both Europe and North America countries (Tombaugh et al., 1999; Tallberg et al., 2008; Stewart et al., 2001; Collie et al., 1999) and from Latin America (del Ser Quijano et al., 2004; Brucki et al., 1997; Acevado et al., 2000). We found that older age and lower educational level corresponded to poorer performances in all four tests and across all sites. The influences of age and educational level on test performances were large, and consistent in size and direction with other norm studies from western countries. Sex had a much weaker influence, and can probably be safely ignored when constructing reference norms. Likewise, while the site by age, education and sex interactions were statistically significant for all cognitive tests, these were very modest effects, and the beta coefficients (Tables 2 to 5) are remarkable mainly for their consistency across sites.

There was a considerable residual effect of site upon cognitive test performance, not accounted for by compositional differences between samples in the distribution of age and education. Further analyses clarified that the between site difference was most parsimoniously accounted for by the effect of region, with smaller effects of rural versus urban location evident for the two memory tests. We should still be cautious about attributing the effect of region to that of language and culture. Firstly, other compositional differences, not directly linked to culture, but relevant to cognitive performance and differently distributed across sites, may not have not been taken into consideration in our analyses. One such effect may be the quality and nature of education received that may not be adequately summarised in terms of level of education (Manly et al., 1999). Second,

while we have included a fairly wide variety of Latin American and Hispanic Caribbean countries and shown fairly consistent norms between them, the norms derived from the Tamil speaking Indians in Tamil Nadu, and the Mandarin-speaking Chinese in and around Beijing clearly cannot be generalised to the vast and diverse populations of India and China as a whole.

By design, the two cognitive tests included in the 10/66 Dementia diagnosis, the CSI'D' COGSCORE and the CERAD WLR, were those that showed the smallest cultural influences and the most robust cross-cultural discriminating properties (Prince et al., 2003). This finding has now been replicated in part in the population-based phase of our study, and is reassuring with respect to the cross-cultural validity of that diagnosis. However, in the light of the findings with respect to other tests, it may be necessary in the future to use region-specific norms in the identification of impairment of memory and verbal fluency for the identification of those meeting cognitive impairment criteria (1.5 standard deviations below the age- and education-specific norms for those with no dementia) for DSM-IV dementia (Prince et al., 2008), and amnestic and non-amnestic mild cognitive impairment. The general effect of such a change would be to lower still further the already negligible prevalence of DSM-IV dementia in Indian sites, and to increase slightly the prevalence of DSM-IV dementia in Chinese sites.

XII. – PREVALENCE, DISTRIBUTION AND POTENTIAL IMPACT OF AMNESTIC MILD COGNITIVE IMPAIRMENT

(Derived from a report under review by PLOS Medicine)

XII.1 Introduction

The majority of older people, and the majority of people with dementia, live in low and middle-income countries (LAMICs). Mild cognitive impairment (MCI) is known to be an important early sign of dementia crucial for targeting and evaluating preventative interventions. However, very little is known about the community prevalence of MCI in LAMIC settings.

In this study, using data from the cross-sectional phase of the 10/66 Dementia Research Group (DRG) programme on dementia, non-communicable diseases and ageing in LAMICs (Prince et al., 2007), we estimated the prevalence of Mayo Clinic defined a-MCI (Petersen et al., 1999), in eleven urban and rural sites in seven countries, and analysed associations with socio-demographic characteristics.

XII.2 Method

XII.2.1 Sample

The analysed sample was as described in Chapter X with the exception that data collection had been completed with an additional site (Puerto Rico), which recently finished its crossectional survey, site that only will be included for this analysis.

XII.2.2 Measures

The following measurements were included in this analysis:

1. The participant interview section of the Community Screening Instrument for Dementia (CSI 'D'). A memory subscale was derived from the CSI 'D' using the items addressing immediate and delayed recall of a three word list, recall of the name of the interviewer, and recall of five elements of a short story (logical memory).

2. The Modified CERAD 10-word-list-learning-task generating an immediate word list memory score with a maximum total of 30 and a word list delayed recall score with a maximum total score of 10.
3. Disability (WHO-DAS)
4. Informant-reported neuropsychiatric symptoms (NPI-Q) were measured and the following binary symptom categories were selected for further analyses: depression, anxiety, apathy, and irritability.
5. Demographic covariates (as defined in Chapter X) were age, gender, education (5 groups), number of assets and illiteracy.
6. Additional health-related covariates: depression (GMS), number of self-reported limiting physical impairments, self-reported hypertension, self-reported stroke, psychotic disorder (GMS), self-reported regular pain.

Case definition of amnestic MCI (aMCI)

Mayo Clinic defined a-MCI was diagnosed based on the following criteria: (1) objective memory impairment beyond that expected for age; (2) subjective memory complaint, preferably confirmed by an informant; (3) no, or only mild impairment in core activities of daily living, and (4) no dementia. Each criterion was operationalized as follows:

Objective memory impairment

A composite memory score was created using results from the memory subscale of the CSI 'D', immediate and delayed word recall scores from the modified CERAD 10 word list. For all tasks impaired performance was defined as a score 1.5 standard deviations or more below the mean adjusted for age and education. Norms were derived from controls without

dementia from the 24-centre 10/66 pilot study (Prince et al., 2007). Participants were excluded if hearing impairment had prevented cognitive assessment.

Subjective memory impairment

An ordinal scale ranging from 0 to 8 was created by summing item scores from relevant questions in the GMS including: 1) Have you had any difficulty with your memory? 2) Have you tended to forget names of your family or close friends/ where you have put things? 3) Do you have to make more efforts to remember things than you used to? Using this scale, subjective memory impairment was defined as present when an individual scored three or more, as defined in previous research.(Ganguli et al., 1996, Kim et al., 2003)

Normal activities of daily living (ADL)/Instrumental Activities of Daily Living (IADL)

Based on responses from the CSI 'D' informant interview, normal ADL/IADLs were defined as very mild or no impairment in either carrying out household chores, pursuing hobbies, using money, feeding, dressing or toileting. The definition of impairment did not include problems arising only from physical impairments.

No dementia

Diagnoses of dementia were applied using the 10/66-dementia algorithm and DSM-IV criteria (Prince et al., 2008). Participants meeting either criterion were excluded from the analysed sample.

XII.2.3 Statistical analysis.

Analyses were carried out on the 10/66 data archive release 3.1. All analyses used STATA version 10.1 (STATA, 2007). As mentioned above, participants with dementia were

excluded from all analyses as has been standard practice in a-MCI epidemiological research. Sample characteristics across countries were described including age, gender, education, number of household assets, global disability scores (WHODAS-12), and NPI-Q symptoms.

In order to determine the potential impact of a-MCI we assumed that, while both ADLs and IADLs would be expected to be intact in people with a-MCI, subtle functional impairment may already be present as well as possibly non-specific and mild BPSD (STATA, 2007). Zero-inflated negative binomial regression (ZINB) count models were used to assess the association between a-MCI and WHODAS-12 disability and NPI-Q scores using identical models to those previously reported for these samples (Fratiglioni and Rocca, 2001). This approach deals with skewness of the dependent variable characterized by excessive zeros (inflation) and distinguishes a group whose members have always zero counts (referred to as "certain zero"), from one in which members have either zero or positive counts. ZINB generates a logistic model for the former group and a negative binomial for the latter, and then combines the two. Log scale coefficients and 95% confidence intervals were back-transformed. We determined the appropriateness of the ZINB model against a standard negative binomial model using the Vuong test post-estimation and adjusted for the relevant covariates listed above, followed by Poisson regression models to generate prevalence ratios for NPI-Q symptoms as binary dependent variables.

Prevalence of a-MCI was reported for each country by age and gender and adjusted for household clustering. Direct standardization, using the whole sample as the reference population, was used to compare prevalence estimates across countries after adjustment for age, gender and education. For each country, associations with age (continuous variable), gender, education (ordinal variable) and number of household assets (ordinal variable) for

a-MCI prevalence were calculated using mutually adjusted (as appropriate) prevalence ratios (PRs), with robust 95% confidence intervals, using Poisson working models.

To determine the pooled effects for all analyses, the statistical outputs for each country were combined into fixed effect meta-analyses. Random effect models were not used as we wished to summarise the countries within this study rather than generalise to a hypothetical population of centres. We then calculated Cochrane Q heterogeneity and Higgins' I^2 (95% CIs). The latter statistics set the degree of heterogeneity between studies that is not explained by chance, and is expressed as a percentage with values up to 25%, 50% and over 75% representing mild, moderate and high heterogeneity, respectively.(Sousa et al., 2009)

XII.3. Results

Sample characteristics

The results were derived from a total of 15,376 participants aged 65+ and without dementia across the different countries. Response rates were higher than 80% in all countries. Missing data on the variables of interest were present in less than 1% of the sample. Descriptive data by country are displayed in Table XII.1. Age was not evenly distributed across groups (65-69; 70-74; 75-79 and 80+ years) across countries, the samples from Venezuela, China and India being slightly younger. In all countries more women participated than men. Educational level was highest in Cuba, and the number of household assets was lowest in Mexico and India.

Table XII.1 Socio demographic characteristics of participants by country

	Cuba	Dominican Rep.	Peru	Venezuela	Mexico	China	India	Puerto Rico
Sample size (n)	2,620	1,767	1,767	1,820	1,821	2,014	1,802	1,765
Response rate (%)	94	95	82	80	85	83	83	93
Age, n (%)								
65-69 years	738(28.2)	511(28.9)	538(30.5)	813(44.7)	537(29.5)	683(33.9)	703(39.0)	398(22.6)
70-74 years	739(28.2)	483(27.3)	475(26.9)	450(24.7)	552(30.3)	634(31.5)	604(33.5)	439(24.9)
75-79 years	582(22.2)	345(19.5)	368(20.8)	320(17.6)	384(21.1)	417(20.7)	290(16.1)	436(24.7)
80+ years	555(21.2)	428(24.2)	386(21.8)	236(13.0)	348(19.1)	280(13.9)	201(11.2)	492(27.9)
Gender (% of females)	1,686(64.4)	1,154(65.3)	1,073(60.7)	1,146(63.0)	1,143(62.8)	1,128(56.0)	974(54.0)	1,183(67.0)
Educational level, n (%)								
No education	54(2.1)	314(17.8)	103(5.8)	133(7.3)	459(25.2)	743(36.9)	935(51.9)	47(2.7)
Some education	548(20.9)	916(51.8)	212(12.0)	408(22.4)	802(44.0)	246(12.2)	411(22.8)	313(17.7)
Complete primary	864(33.0)	338(19.1)	654(37.0)	913(50.2)	337(18.5)	532(26.4)	301(16.7)	356(20.2)
Complete secondary	681(26.0)	126(7.1)	486(27.5)	262(14.4)	117(6.4)	358(17.8)	110(6.1)	661(37.5)
Complete tertiary	468(17.9)	66(3.7)	301(17.0)	92(5.1)	104(5.7)	135(6.7)	43(2.4)	383(21.7)
Three assets or fewer, n (%)	67(2.6)	256(14.5)	83(4.7)	33(1.8)	373(20.5)	104(5.2)	918(51.0)	4(0.2)
Neuropsychiatric symptoms, n (%)								
Depression	117(4.5)	220(12.5)	86(4.9)	84(4.6)	73(4.0)	3(0.2)	139(7.7)	36(2.0)
Anxiety	158(6.0)	233(13.2)	199(11.3)	263(14.5)	121(6.6)	7(0.4)	77(4.3)	101(5.7)
Apathy	117(4.5)	226(12.8)	93(5.3)	138(7.7)	165(9.1)	15(0.7)	18(1.0)	58(3.5)
Irritability	583(22.5)	412(23.3)	381(21.6)	383(21.3)	434(23.9)	26(1.3)	227(12.6)	254(15.2)
WHO-DAS 12, mean (sd)	9.69(14.2)	13.91(17.3)	9.36(14.3)	9.18(13.8)	8.59(15.3)	5.30(12.0)	17.44(17.2)	12.13(16.6)
WHO-DAS 12, mean (sd) omitting zeros	16.55(15.2)	21.11(17.3)	15.91(15.7)	16.18(14.8)	18.03(17.9)	18.39(16.1)	22.19(16.4)	21.33(17.0)

WHO-DAS 12: disability assessment schedule, 12-items; NPI-Q severity: total severity in neuro-psychiatric inventory. **SD=** Standard Deviation.

Associations between a-MCI and impact measures

In each country there was a statistically significant zero-inflation in the distributions of WHODAS 12 scores (Vuong test for the whole sample, $z=45.29$ $p<0.001$) that confirmed the better fit of ZINB over negative binomial alone. Associations between a-MCI, disability and neuropsychiatric symptoms are summarized in Table XII.2 along with meta-analytical fixed-effect method pooled estimates, and between-country heterogeneity.

After adjustment, disability was significantly higher in a-MCI cases compared to the remainder in Peru, India and Dominican Republic, although was lower in China. The pooled fixed-effect model meta-analytical estimate indicated a positive association with disability although there was moderate to high heterogeneity in these associations between countries.

After adjustment, a-MCI cases were more likely to have informant-rated anxiety, irritability and apathy symptoms, with no significant between-country heterogeneity. However, there was no overall association with informant-rated depression in pooled estimates although the individual prevalence ratio was significant in Peru.

Table XII.2 Associations between aMCI and disability (WHO-DAS 12) and aMCI and neuropsychiatric symptoms (NPI-Q) (depression, anxiety, apathy, irritability)

	ZINB* (95% CI)	Adjusted[1] PRs (95% CI)			
Individual study site estimates	**WHO-DAS 12[1]**	**Depression[2]**	**Anxiety**	**Apathy**	**Irritability[2]**
Cuba	0.93(0.74-1.19)	0.96(0.23-3.93)	1.74(0.77-3.94)	1.66(0.59-4.67)	0.84(0.44-1.57)
Dominican Republic	1.49(1.08-2.06)	1.04(0.47-2.30)	1.75(1.00-3.05)	1.54(0.76-3.12)	0.98(0.52-1.82)
Peru	1.51(1.17-1.94)	2.14(1.01-4.54)	1.54(0.89-2.65)	1.38(0.57-3.33)	1.28(0.83-1.96)
Venezuela	0.92(0.53-1.60)	2.14(0.47-9.74)	2.49(1.40-4.42)	3.59(1.94-6.65)	1.74(1.06-2.86)
Mexico	1.12(0.78-1.62)	1.07(0.35-3.29)	1.59(0.76-3.31)	0.79(0.35-1.82)	1.11(0.73-1.69)
China[3]	0.67(0.45-0.99)	NC	NC	10.2(1.40-74.5)	9.90(2.57-38.0)
India	1.20(1.03-1.40)	0.69(0.31-1.53)	0.81(0.25-2.57)	1.18(0.13-10.8)	1.27(0.82-1.98)
Puerto Rico	1.05(0.87-1.27)	2.60(0.90-7.54)	1.85(0.98-3.49)	1.68(0.65-4.34)	1.04(0.61-1.76)
Pooled meta-analysis (fixed effect method) [4]					
Combined estimate	1.13(1.04-1.23)	1.31(0.91-1.89)	1.75(1.37-2.25)	1.83 (1.33-2.51)	1.24(1.03-1.49)
Test for heterogeneity p-value	0.008	0.344	0.753	0.091	0.058
I^2 Higgins (95% CI)	63%(20-83)	11%(0-74)	0%(0-71)	43%(0-75)	49%(0-77)

*Exponentiated coefficients from zero inflated negative binomial (ZINB) models representing increase in disability of aMCI participants compared to normal. Zero inflation fitted using age, gender, educational level, number of household assets, depression, arthritis, visual problems, hearing problems, cough and breathing problems, heart problems, gastrointestinal problems, fainting, limb and skin problems, hypertension and stroke. **MCI=** Mild Cognitive Impairment, **WHO-DAS 12=** World Health Organization - Disability Assessment Schedule, **NPI-Q=** Neuropsychiatric Inventory Questionnaire, **CI=** Confidence Interval, **PRs=** Prevalence Ratios

[1] Adjusted for age, gender, and educational level, number of household assets and of physical limiting impairments, psychosis and stroke.
[2] Depression and irritability were additionally adjusted for pain.
[3] China was not adjusted for psychosis
[4] The pooled fixed-effect model meta-analytical estimate for depression and anxiety were done without China
WHO DAS 12: WHO disability assessment schedule, 12 items; NPI Q: Neuro Psychiatric Index; NC: not calculable due to zero cell sizes

Prevalence and correlates of a-MCI and variation between countries

The crude prevalence of a-MCI ranged from 0.8% in China to 4.3% in India. Country differences changed little (range: 0.6-4.6%) after standardization for age, gender and education level, as displayed in Table XII.3.

Adjusted prevalence ratios (PRs) (95% CI) from Poisson regression models for independent associations with age, gender, education and assets are shown in Table XII.4. No pooled associations were found with age or education but there was a modest association with male gender and fewer assets. Overall little heterogeneity was found between nations in these associations.

Table XII. 3 Prevalence of amnestic mild cognitive impairment (a-MCI) by country, gender and age group

	a-MCI prevalence, % (95% CI)				Crude prevalence (95% CI) All age groups	Standardized prevalence (95%CI)* All age groups
	65-69 years	70-74 years	75-80 years	80+ years		
Cuba (n)	738	739	582	555	1.8(1.3-2.3)	1.5(1.0-1.9)
Males	1.5(0.0-3.0)	1.8(0.2-3.4)	0.0(0.0-0.0)	1.7(-0.2-3.6)		
Females	2.7(1.3-4.2)	2.6(1.1-4.0)	1.6(0.3-2.9)	0.8(-0.1-1.7)		
Dominican Rep. (n)	511	483	345	428	1.4(0.9-2.0)	1.3(0.7-1.8)
Males	1.7(-0.2-3.6)	2.2(0.0-4.4)	2.7(-0.4-5.7)	2.9(0.1-5.7)		
Females	0.9(-0.1-1.9)	1.7(0.2-3.1)	0.4(-0.4-1.3)	0.7(-0.3-1.7)		
Peru (n)	538	475	368	386	3.1(2.3-3.9)	2.6(1.9-3.3)
Males	5.4(2.1-8.6)	2.7(0.3-5.1)	2.1(-0.3-4.5)	4.4(1.4-7.4)		
Females	2.3(0.7-3.8)	1.7(0.2-3.2)	3.6(1.1-6.0)	3.4(0.9-5.9)		
Venezuela (n)	813	450	320	236	1.2(0.7-1.7)	1.0(0.7-1.4)
Males	1.3(0.0-2.6)	0.0(0.0-0.0)	2.6(-0.3-5.5)	0.0(0.0-0.0)		
Females	1.6(0.5-2.7)	1.4(0.0-2.9)	1.5(-0.2-3.1)	0.0(0.0-0.0)		
Mexico (n)	537	552	384	348	3.2(2.4-4.1)	2.8(2.0-3.6)
Males	3.7(0.8-6.7)	4.3(1.5-7.0)	5.1(1.6-8.6)	4.0(0.8-7.2)		
Females	1.3(0.2-2.5)	4.1(2.0-6.2)	3.9(1.4-6.5)	1.0(-0.4-2.4)		
China (n)	683	634	417	280	0.8(0.4-1.2)	0.6(0.3-0.9)
Males	1.0(-0.1-2.1)	0.4(-0.3-1.1)	1.7(-0.2-3.6)	0.0(0.0-0.0)		
Females	1.3(0.2-2.4)	0.6(-0.2-1.4)	0.8(-0.3-2.0)	0.7(-0.6-2.0)		
India (n)	703	604	290	201	4.3(3.3-5.2)	4.6(3.7-5.4)
Males	7.0(4.1-9.9)	3.8(1.5-6.1)	4.8(1.3-8.3)	1.0(-1.0-2.9)		
Females	3.3(1.5-5.0)	4.4(2.2-6.6)	5.6(1.8-9.5)	1.1(-1.1-3.2)		
Puerto Rico (n)	398	439	436	492	3.9(3.0-4.8)	3.0(2.2-3.8)
Males	3.9(0.1-7.8)	5.5(1.7-9.2)	4.1(0.8-7.3)	5.5(2.2-8.9)		
Females	4.4(2.1-6.8)	3.4(1.3-5.5)	3.5(1.3-5.6)	2.3(0.6-3.9)		

a-MCI= Amnestic Mild Cognitive Impairment, **CI=**Confidence Interval

*Direct standardization for age gender and educational level using the whole sample as the standard population.

Table XII.4 Mutually adjusted prevalence ratios (PRs) (95% CI) for the independent effects of age, gender, education and assets on amnestic mild cognitive impairment (aMCI) prevalence.

	Adjusted[1] PRs (95% CI)			
	Age (per year increment)	**Gender** (males vs. females)	**Education** (more vs. less years)	**Assets** (more vs. less)
Individual study site estimates				
Cuba	0.97(0.92-1.02)	0.63(0.33-1.21)	0.95(0.72-1.24)	1.52(1.00-2.30)
Dominican Republic	1.03(0.97-1.09)	2.25(1.04-4.86)	1.27(0.83-1.96)	0.82(0.63-1.06)
Peru	1.03(0.99-1.07)	1.29(0.75-2.22)	1.08(0.82-1.42)	0.81(0.64-1.03)
Venezuela	0.95(0.88-1.02)	0.79(0.33-1.90)	0.91(0.55-1.52)	0.97(0.83-1.14)
Mexico	1.01(0.97-1.04)	1.57(0.94-2.60)	1.24(0.95-1.61)	0.81(0.69-0.95)
China	0.97(0.88-1.06)	1.00(0.40-2.51)	0.86(0.64-1.15)	0.80(0.50-1.27)
India	0.97(0.94-1.01)	1.19(0.74-1.93)	1.14(0.89-1.47)	0.85(0.72-0.99)
Puerto Rico	0.99(0.95-1.02)	1.46(0.91-2.33)	1.04(0.86-1.26)	0.94(0.70-1.27)
Pooled meta-analysis (fixed effect method)				
Combined estimate	0.99 (0.98-1.01)	1.25 (1.01-1.54)	1.06 (0.96-1.16)	0.88 (0.82-0.95)
Test for heterogeneity	0.209	0.25	0.619	0.168
Higgins (95% CI)	27% (0-67)	23% (0-64)	0% (0-68)	33% (0-70)

1 Mutually adjusted for age, educational level, gender and number of assets as appropriate

PRs= Prevalence Ratios, **CI=** Confidence Interval, **a-MCI=** Amnestic Mild Cognitive Impairment

XII.4 Discussion

Using data from a large series of cross-sectional surveys applying standard sampling and measurements, we estimated the community prevalence of Mayo clinic defined a-MCI in six countries in Latin America, and in China and India. To our knowledge this is the first study to attempt to make direct comparisons of prevalence estimates of a-MCI across diverse cultures and world regions.

Differences in prevalence between countries were marked and ranged from 0.8% (China) to 4.3% (India) – i.e. greater than five-fold variation. After direct standardization for age, gender and education, using the whole population as the reference, these differences were not markedly attenuated. Inconsistencies in a-MCI prevalence observed between the 10/66 study centres are likely to be due to components of the a-MCI diagnosis itself. In a cross-cultural context, these support questions previously raised concerning its conceptual basis (Higgins and Thompson, 2002) and/or operationalization outside clinical settings (Ritchie and Touchon, 2000).

Sample characteristics should be considered first, however, and one possible reason for heterogeneity is survival bias. The broader category of MCI has been reported to be associated with increased mortality in a prospective study (Hunderfund et al., 2006) and differences in aMCI-associated survival between country sites cannot be excluded as a factor influencing variation in prevalence.

A second important issue concerns the ability to separate MCI constructs from dementia in epidemiological samples, particularly in a cross-cultural context. It should be noted that the 10/66-dementia diagnosis showed much higher sensitivity than the DSM-IV criteria in both

pilot and clinical validation 10/66 studies (Prince et al., 2008, Prince et al., 2007). While the capability to detect early dementia cases represents an undoubted strength of the 10/66-dementia criteria, it cannot be excluded that it may have been responsible of the unusually low a-MCI prevalence we have observed, by systematically lowering the hypothetical line between MCI syndromes and dementia.

Compared to a-MCI prevalence reports from community based sites in Finland (5.3%) (Ganguli et al., 2004) Italy (7% and 7.7%), (Matthews et al., 2007, Manly et al., 2005) Japan (4.9%) (Di Carlo et al., 2007) and the USA (6%) (Palmer et al., 2003) both the crude and adjusted a-MCI prevalence reported here are relatively low. However, the estimates are similar to those reported by the British MRC CFAS study (2.5%) (Meguro et al., 2004) to the prevalence of cognitive impairment not dementia in the Canadian Study of Health and Ageing (Matthews et al., 2008) and to estimates for a-MCI prevalence in community samples from France (3.2%) (Graham et al., 1997), the USA (3.5%) (Busse et al., 2003b) and Germany (3%) (Ritchie et al., 2001). Low a-MCI prevalence in our Latin American sites contrast with the a-MCI prevalence (ranging between 3.8-6.3% depending on age) reported amongst American Caribbean Hispanics (Hanninen et al., 2002). As described above, differential mortality may explain these differences, but a potential role of the environment and lifestyle in the increased risk of a-MCI amongst Hispanic immigrants in North America cannot be excluded. Crude a-MCI prevalence in the Indian 10/66 sites (4.3%) is similar to the figure described by Das and colleagues in Northern India (Ritchie et al., 2001). Prevalence in China was the lowest (0.6%) but similar to that described in the VITA study in Vienna (Busse et al., 2003a). To our knowledge no Chinese studies on MCI or a-MCI prevalence have been published to compare with our results although screening instruments to detect MCI cases have been validated for use in the general Chinese

population.(Jungwirth et al., 2005, Lam et al., 2008) Overall, the results suggest that there is very little consistency in prevalence of a-MCI across world regions. This may possibly reflect diagnostic issues relating to a lack of specific criteria for the operationalization of MCI (i.e. cognitive batteries and specific cut-off scores for impairment) as well as unmeasured differences and cultural variations potentially relevant for some components of the a-MCI construct (i.e. subjective memory impairment, as described below).

Female gender, increased age, lower education and lower socio-economic status are associated with dementia (Li et al., 2006) and have been described in association with MCI (Hanninen et al., 2002). In our study however, the effects of age and education on a-MCI prevalence were negligible across study sites, with no between-country heterogeneity in this respect. For education, this might reflect lower variance in the exposure or weaker underlying associations between education and other risk factor profiles in these samples. Lower socioeconomic status remained associated with a-MCI and this may be a better marker than education of relevant social disadvantage in this group. However, it is important also to bear in mind that education-adjusted norms were used to apply cognitive impairment criteria for the a-MCI diagnosis and the similarities between education groups may be artefact. The negative results for age may represent the same phenomenon, but could also possibly reflect a more rigorous exclusion of dementia in our samples with early cases responsible for age-MCI associations in other settings. The observed association with male gender contrasts with the higher reported age-adjusted prevalence of dementia in women compared to men (Fratiglioni et al., 2007), could again reflect the effect of dementia case exclusion or could suggest, as the Mayo Clinic Study of Aging reports that "women transition from normal cognition directly to dementia at a later age but more abruptly" (Petersen et al., 2010).

A key consideration with a-MCI applied as a construct in international research is its cross-cultural validity. An advantage of the 10/66 study is that, identical measures were taken and identical algorithms applied for diagnosis across the study sites and the protocols for cognitive assessments in the 10/66 study were the result of a long and painstaking process of development and validation (Prince et al., 2007). Associations with disability and neuropsychiatric symptoms across sites can be viewed as further evidence for the validity of the construct since these are comparable with findings from other community samples (STATA, 2007, Okura et al., 2010). Heterogeneity in these associations between countries was also relatively low, providing further support for the cross-cultural applicability of the a-MCI construct as well as supporting evidence from other research for its potential impact, although cause and effect relationships cannot be inferred from the cross-sectional findings of this specific analysis.

Strengths of the study include the very large sample size and the wide range of populations sampled in terms of culture, economy and population characteristics. Moreover, internal validity was maintained through rigorously pre-validated and standardised measurements applied consistently between countries in addition to common algorithms used to define a-MCI. There are some limitations. The samples were drawn from specific geographic catchment areas and cannot be assumed to be representative of the source nation/site. The study was cross-sectional in design and the impact of survival cannot be evaluated. Furthermore, within the a-MCI category, participants who had developed this late in life could not be distinguished from those for whom it was a stable lifetime trait. Finally, a-MCI diagnosis was determined without clinical judgment, which is difficult to obtain in large population-based studies and unfeasible in most of our study sites. Although a-MCI was originally derived as a diagnosis for secondary or tertiary care clinical settings, it is

being increasingly applied in epidemiological research and data from community samples is an important supplement, particularly if future community-level interventions are planned to prevent progression to dementia. Our analysis here is intended to extend this particular evidence base. Follow-up is currently underway in most 10/66 sites which will provide further data on predictive validity.

XIII. SUBJECTIVE MEMORY COMPLAINTS PREVALENCE AND CORRELATES

XIII.1 Introduction

As discussed in Chapter V, subjective memory complaints (SMCs) in everyday life and those reported in clinical settings are frequent among older people, although their prevalence, correlates, diagnostic definition, predictive value and clinical meaning remains controversial (Mitchell, 2008).

SMCs reveal an individual´s awareness of and belief about their own cognitive competence in everyday life (Grut et al., 1993); they assess everyday memory and cognitive problems that may not be captured by standardized neuropsychological tests, thus providing clinicians another perspective on understanding memory and cognitive function in old age (Chung and Man, 2009). They are also a central component of many MCI or equivalent construct criteria.

The aim of the analyses described in this chapter was to investigate SMC prevalence and associations in the 10/66 samples, in order to understand better the particular relationship between subjective and objective impairment in low and middle-income countries (LAMICs) where there is a dearth of information.

XIII.2 Method

XIII.2.1 Sample

The analysed samples were those described in Chapter X

XIII.2.2 Measures

The following measures were used in this analysis:

1. SMC was ascertained using responses to three questions assessing four relevant symptoms; these questions formed part of the Geriatric Mental State Examination (GMS) but do not contribute significantly to the AGECAT algorithm output.

   i. Have you had any difficulty with your memory?

   ii. Have you tended to forget things?

      a. Names of your family or close friends?

      b. Where you have put things?

   iii. Do you have to make more effort to remember things than you used to?

Symptoms i, iia and iib were rated as 0 (normal), 1(abnormal but mild to moderate intensity or infrequent or fleeting), or 2 (abnormal and severe, frequent or persistent). Symptom iii was rated as simply absent (0) or present (1). Item scores were summed to form an *ad hoc* ordinal scale with a maximum possible score of 7. As in previous research using this particular scale, a participant was considered to have SMC on the basis of a score of three or above (Kim et al., 2003, Stewart et al., 2001b).

2. For this analysis we considered the following socio-demographic measures as independent variables: gender, participants' age (divided into two groups: <75 and =>75 years old) and education level (5 groups as previously described). A dichotomous variable was created for number of household assets on the basis of three/less assets, or four/more assets. Participants were also defined as living alone or not.

3. Cognitive function was measured using the following variables

   a) CSI-D COGSCORE

   b) Verbal fluency (animal naming)

   c) CERAD 10-word list learning task immediate recall

d) CERAD 10-word list learning task delayed recall

4. Depression was determined according to the GMS AGECAT depression diagnosis.

5. All those meeting criteria for either 10/66 dementia (Prince et al., 2003), or DSM-IV dementia (Prince et al., 2008) were classified as dementia cases.

6. Any need for care was defined from screening items in the informant questionnaire.

7. Disability was defined on the basis of an above 90th percentile score on the 12-item World Health Organization Disability Assessment Schedule version 2.0 (WHODAS 2.0).

XIII.2.3 Statistical Analysis

Analyses were carried out on the 10/66 data archive release 2.6, using STATA version 10.1. Global prevalence (combined samples) of SMC was described and then investigated in relation to age group, gender, educational level, assets, living alone, depression, dementia, need of care, disability, and cognitive functioning, using odds rations (ORs) with 95% confidence intervals and p-values from chi squared tests. The summary prevalence stratified by site was described for the whole sample and then separately by dementia status. Logistic regression models were used to describe further the association between SMC and the measures of cognitive function by site in participants without dementia, using three grouped models (unadjusted; adjusted for socio-demographic characteristics; and adjusted for socio-demographic and clinical characteristics). To determine the overall association between SMC and measured cognitive function, findings for the eleven study sites were combined by fixed effect meta-analyses and the degree of heterogeneity was estimated

using Cochrane Q and Higgins' I^2 (95% CI) (Higgins and Thompson, 2002) tests. The same procedures were carried out to investigate and compare associations between SMC and dementia.

XIII.3. Results

Analyses of SMC correlates in the pooled sample from all sites are summarized in Table XIII.1. SMCs were significantly associated with older age, females, fewer assets, living alone status, depression, dementia, need for care, and disability. Lower function on all four cognitive measures was also associated with SMC. No association, however, was found with education status.

Table XIII.2 summarizes the prevalence of SMC by site and dementia status. The overall SMC prevalence was 33.5% and varied between the sites from 6.6% in rural China to 45.5% in rural Mexico, with prevalences in most of the remaining sites approximately one-third, with the exception of urban settings in Peru (45.4%) and urban China (25.3%).

In participants without dementia to the overall prevalence was 31.2% with the lowest prevalence again found in rural China (3.9%) and the highest in Peru (44%), followed by rural Mexico (43.6%).

In participants with dementia, the prevalence of SMC was more consistent, with between 50-75% of these participants reporting SMC in most sites: highest in China and Venezuela and lowest in Dominican Republic.

Table XIII.1 Prevalence of subjective memory complaints (SMC) stratified by socio-demographic and relevant clinical characteristics in the pooled 10/66 samples.

Variable	Categories	Number	%SMI	OR(95%IC)
Age group (years)	65-74	8,775	30.1	1
	75+	5,986	37.3	1.33 (1.24-1.43)
Gender	Male	5,640	29.2	1
	Female	9,094	36.0	1.37 (1.47-1.28)
Education	None	3,106	33.1	1.16 (1.01-1.34)
	Some	3,871	37.4	1.4 (1.22-1.61)
	Completed primary	4,230	32.2	1.12 (0.97-1.28)
	Completed secondary	2,231	30.1	1.05 (0.91-1.23)
	Completed tertiary	1,263	29.9	1
Assets	More than 3	12,698	32.8	1
	3 or less	2,061	37.7	1.24 (1.12-1.37)
Living alone	No	13,634	33.2	1
	Yes	1,142	36.7	1.17 (1.03-1.32)
Depression	Absent	10,140	25.1	1
	Present	4,636	51.7	3.19 (2.97-3.44)
Dementia	Absent	13,589	31.2	1
	Present	1,187	59.7	3.28 (2.90-3.70)
Need for care	No	13,163	32.2	1
	Yes	1,240	47.3	1.89 (1.68-2.13)
Disability (WHODAS)	Below 90th percentile	13,421	31.8	1
	90th percentile or higher	1,216	49.5	2.1 (1.87-2.36)
Global cognitive functioning (CSI-D cog score)	Quartile 4	3,750	23.1	1
	Quartile 3	3,728	29.5	1.39 (1.25-1.55)
	Quartile 2	3,767	37.3	1.99 (1.79-2.20)
	Quartile 1	3,531	44.6	2.69 (2.43-2.98)
Verbal fluency (animal naming)	Quartile 4	3,004	25.4	1
	Quartile 3	4,321	29.4	1.22 (1.1 -1.36)
	Quartile 2	3,544	37.3	1.75 (1.57-1.94)
	Quartile 1	3,907	40.8	2.03 (1.82-2.25)
Immediate recall (CERAD word list)	Quartile 4	3,265	24.1	1
	Quartile 3	3,254	27.2	1.18 (1.05-1.32)
	Quartile 2	4,547	34.8	1.68 (1.52-1.87)
	Quartile 1	3,705	45.6	2.65 (2.38-2.94)
Delayed Recall (CERAD word list)	Quartile 4	2,562	24.3	1
	Quartile 3	4,694	30.3	1.36 (1.21-1.52)
	Quartile 2	2,608	33.2	1.55 (1.37-1.75)
	Quartile 1	4,912	41.4	2.19 (1.97-2.45)

SMC= Subjective Memory complaints, **OR=** Odds Ratio, **CI=** Confidence Interval, **WHO-DAS=** World Health Organization - Disability Assessment Schedule, **CSI-D=** Community Screening Interview for Dementia, **SMI=** Subjective Memory Impairment, **CERAD=** Consortium to establish a registry for Alzheimer Disease

Table XIII.2 Subjective memory complaints (SMC) prevalence by site and dementia diagnosis

Site	With dementia		Without dementia		Total sample	
	Number	SMC prevalence (%)	Number	SMC prevalence (%)	Number	SMC prevalence (%)
Cuba	283	55.5	2,617	30.9	2,900	33.3
Dominican Rep	226	45.1	1,769	29.4	1,995	31.2
Peru Urban	90	64.4	1,249	44.0	1,339	45.4
Peru Rural	34	67.6	514	31.3	548	33.6
Venezuela	134	73.9	1,811	33.8	1,945	36.6
Mexico Urban	91	63.7	909	33.6	1,000	36.3
Mexico Rural	84	66.7	911	43.6	995	45.5
China Urban	52	71.1	1,074	23.1	1,126	25.3
China Rural	38	73.7	936	3.9	974	6.6
India Urban	72	59.7	929	33.2	1,001	35.1
India Rural	83	57.8	870	33.5	953	35.6
Total	**1,187**	**59.7%**	**13,589**	**31.2%**	**14,776**	**33.5%**

SMC= Subjective Memory complaints

Findings of compared sites, unadjusted and adjusted associations between SMC and cognitive function of participants without dementia, are summarized in Tables XIII 3-6. For global cognitive function (CSI-D 'cogscore'; Table XIII.3) associations in the unadjusted model were strongest for rural China (OR 3.67), weakest where still significant for the Dominican Republic (OR 1.18) and absent in the two Indian sites; in the partially adjusted model 2, most of the associations remained similar in strength apart from urban Peru. In the fully adjusted model 3, which included depression and need for care, associations in most sites again remained relatively stable, apart from Dominican Republic. Between-site heterogeneity remained relatively high, as indicated by I^2 values greater than 85%.

Table XIII. 3 – Site-specific associations between lower global cognitive function and subjective memory complaints (SMC) in participants without dementia.

Site	Odds ratio (95% CI) for SMC per descending quartile of CSI-D cog score		
	Model 1	Model 2	Model 3
Cuba	**1.32 (1.22-1.43)**	**1.35 (1.23-1.48)**	**1.32 (1.191.47)**
Dominican Republic	**1.18 (1.07-1.30)**	**1.14 (1.02-1.28)**	1.07 (0.95-1.21)
Peru (urban)	**1.20 (1.06-1.35)**	1.12 (0.98-1.29)	1.04 (0.90-1.21)
Peru (rural)	**1.51 (1.22-1.85)**	**1.39 (1.11-1.75)**	**1.37 (1.08-1.73)**
Venezuela	**1.36 (1.23-1.51)**	**1.30 (1.16-1.46)**	**1.20 (1.06-1.35)**
Mexico (urban)	**1.47 (1.28-1.69)**	**1.51 (1.29-1.77)**	**1.48 (1.26-1.74)**
Mexico (rural)	**1. 30(1.12-1.50)**	**1.29 (1.09-1.51)**	**1.25 (1.06-1.47)**
China (urban)	**2.05 (1.73-2.42)**	**2.21 (1.84-2.66)**	**2.23 (1.82-2.71)**
China (rural)	**3.67 (2.44-5.53)**	**4.17 (2.69-6.46)**	**3.48 (2.16-5.59)**
India (urban)	1.04 (0.91-1.18)	0.99 (0.85-1.16)	0.99 (0.83-1.17)
India (rural)	0.88 (0.73-1.05)	**0.68 (0.54-0.86)**	0.90 (0.65-1.24)
Pooled meta analysis			
Combined estimate Test for overall effect	**1.30** **(1.25-1.35)**	**1.28** **(1.22-1.34)**	**1.25** **(1.19-1.31)**
Heterogeneity Q DF p value	93.404 10 **0.000**	114.215 10 **0.000**	79.890 10 **0.000**
I^2 Higgins (95% CI)	89 % (83-98)	91% (86-94)	87% (80-92)

Model 1 = Unadjusted
Model 2 = Adjusted for age, gender and education.
Model 3 = Adjusted for age, gender, education, assets, living alone, depression, need of care and disability.
CI= Confidence Interval, **CSI-D=** Community Screening Interview for Dementia

For verbal fluency (Table XIII.4), the strongest association was found in the rural China site (OR 2.16) with absent/weak associations in the Indian sites, as with the global cognitive outcome as well as in Venezuela and Dominican Republic. As previously observed, there was little change in most coefficients after adjustments and high, although slightly weaker, between-site heterogeneity.

Table XIII. 4 – Site-specific associations between lower verbal fluency and subjective memory complaint (SMC) in participants without dementia.

Site	Odds ratio (95% CI) for SMC per descending quartile of verbal fluency score (animal naming)		
	Model 1	Model 2	Model 3
Cuba	**1.37 (1.26-1.48)**	**1.35 (1.24-1.48)**	**1.31 (1.19-1.44)**
DR	1.08 (0.97-1.21)	1.04 (0.93-1.16)	1.01 (0.90 -1.13)
Peru (urban)	**1.22 (1.08-1.38)**	**1.17 (1.03-1.33)**	**1.16 (1.01-1.32)**
Peru (rural)	**1.28 (1.04-1.58)**	1.22 (0.97-1.53)	1.20 (0.96-1.52)
Venezuela	1.05 (0.95-1.16)	1.00 (0.89-1.12)	0.98 (0.87-1.10)
Mexico (urban)	**1.50 (1.30-1.73)**	**1.48 (1.27-1.72)**	**1.45 (1.24-1.70)**
Mexico (rural)	**1.21 (1.05-1.40)**	**1.18 (1.02-1.37)**	**1.17 (1.01-1.36)**
China (urban)	**1.70 (1.45-2.00)**	**1.68 (1.43-1.99)**	**1.64 (1.38-1.94)**
China (rural)	**2.16 (1.58-2.93)**	**2.20 (1.59-3.03)**	**2.18 (1.52-3.14)**
India (urban)	1.12 (0.88-1.41)	1.12 (0.87-1.43)	0.99 (0.77-1.29)
India (rural)	1.13 (0.93-1.38)	1.09 (0.89-1.34)	1.10 (0.83-1.45)
Pooled meta analysis			
Combined estimate Test for overall effect	**1.26** **(1.21-1.31)**	**1.22** **(1.17-1.28)**	**1.19** **(1.14-1.25)**
Heterogeneity Q	57.904	60.219	55.193
DF	10	10	10
p value	**0.000**	**0.000**	**0.000**
I^2 Higgins (95% CI)	83% (70- 90)	83% (72-90)	82% (69-89)

Model 1 = Unadjusted
Model 2 = Adjusted for age, gender and education.
Model 3 = Adjusted for age, gender, education, assets, living alone, depression, need of care and disability.
SMC= Subjective Memory complaints, **CI=** Confidence Interval, **DR=** Dominican Republic

For immediate recall (Table XIII.5) and delayed recall (Table XIII. 6), the strongest associations continued to be found in the Chinese sites, similar to the findings for global function and verbal fluency, although were stronger in India than observed for the other tests, being most consistently weak in Venezuela and rural Mexico. High between-site heterogeneity was found.

Table XIII.5 – Site-specific associations between lower immediate word list recall and subjective memory complaint (SMC) in participants without dementia.

Site	Odds ratio (95% CI) for SMC per descending quartile of CERAD immediate word list recall score		
	Model 1	Model 2	Model 3
Cuba	**1.40 (1.28-1.52)**	**1.43 (1.31-1.57)**	**1.35 (1.22-1.49)**
DR	**1.35 (1.21-1.50)**	**1.36 (1.21-1.52)**	**1.27 (1.13-1.42)**
Peru (urban)	**1.29 (1.16-1.45)**	**1.29 (1.14-1.47)**	**1.24 (1.09-1.42)**
Peru (rural)	1.16 (0.93-1.43)	1.05 (0.83-1.33)	1.05 (0.83-1.33)
Venezuela	1.07 (0.97-1.18)	1.06 (0.95-1.18)	1.02 (0.91-1.14)
Mexico (urban)	**1.57 (1.35-1.83)**	**1.57 (1.33-1.86)**	**1.59 (1.34-1.88)**
Mexico (rural)	1.07 (0.93-1.23)	1.07 (0.93-1.25)	1.04 (0.89-1.20)
China (urban)	**2.25 (1.92-2.64)**	**2.38 (2.01-2.83)**	**2.32 (1.94-2.76)**
China (rural)	**6.90 (3.40-14.0)**	**6.75 (3.25-14.0)**	**6.10 (2.79-13.3)**
India (urban)	**1.27 (1.11-1.46)**	**1.31 (1.13-1.52)**	**1.18 (1.01-1.38)**
India (rural)	**1.33 (1.02-1.74)**	1.28 (0.98-1.67)	1.34 (0.95-1.90)
Pooled meta analysis			
Combined estimate Test for overall effect	**1.32** **(1.27-1.38)**	**1.34** **(1.28-1.40)**	**1.28** **(1.22-1.33)**
Heterogeneity Q DF p value	99.14 10 **0.000**	99.07 10 **0.000**	93.53 10 **0.000**
I^2 Higgins (95% CI)	90% (84-94)	90% (84-94)	89% (83-93)

Model 1 = Unadjusted
Model 2 = Adjusted for age, gender and education.
Model 3 = Adjusted for age, gender, education, assets, living alone, depression, need of care and disability.
SMC= Subjective Memory complaints, **CI=** Confidence Interval, **CERAD**= Consortium to establish a registry for Alzheimer Disease, **DR=** Dominican Republic, **QDF=** Ratio of Cochran Q and Degrees of Freedom

Table XIII. 6 Site-specific associations between lower delayed word list recall and subjective memory complaint (SMC) in participants without dementia.

Site	Odds ratio (95% CI) for SMC per descending quartile of CERAD delayed word list recall score		
	Model 1	Model 2	Model 3
Cuba	**1.25 (1.15-1.35)**	**1.27 (1.17-1.38)**	**1.21 (1.10-1.33)**
DR	**1.33 (1.20-1.47)**	**1.33 (1.20-1.48)**	**1.29 (1.15-1.44)**
Peru(urban)	**1.17 (1.05-1.30)**	**1.14 (1.01-1.28)**	1.12 (0.99-1.26)
Peru (rural)	**1.25 (1.03-1.52)**	1.19 (0.97-1.46)	1.18 (0.96-1.45)
Venezuela	1.02 (0.92-1.13)	1.02 (0.92-1.13)	0.99 (0.89-1.10)
Mexico (urban)	**1.50 (1.31-1.71)**	**1.48 (1.28-1.71)**	**1.46 (1.26-1.69)**
Mexico (rural)	1.06 (0.93-1.20)	1.06 (0.92-1.22)	1.04 (0.91-1.19)
China (urban)	**2.09 (1.76-2.48)**	**2.11 (1.76-2.52)**	**2.07 (1.71-2.50)**
China (rural)	**3.06 (1.59-5.89)**	**3.01 (1.52-5.96)**	**3.35 (1.55-7.24)**
India (urban)	1.13 (0.99-1.28)	1.13 (0.99-1.29)	1.08 (0.94-1.25)
India (rural)	**1.22 (1.01-1.47)**	1.17 (0.97-1.42)	1.21 (0.95-1.55)
Pooled meta analysis			
Combined estimate Test for overall effect	**1.24** **(1.19-1.28)**	**1.23** **(1.18-1.28)**	**1.19** **(1.15-1.25)**
Heterogeneity Q	76.766	72.404	67.106
DF	10	10	10
p value	**0.000**	**0.000**	**0.000**
I^2 Higgins (95% CI)	87% (79-92)	86% (77-92)	85% (75-91)

Model 1 = Unadjusted
Model 2 = Adjusted for age, gender and education.
Model 3 = Adjusted for age, gender, education, assets, living alone, depression, need of care and disability.
SMC= Subjective Memory complaints, **CI=** Confidence Interval, **CERAD**= Consortium to establish a registry for Alzheimer Disease, **DR=** Dominican Republic, **QDF=** Ratio of Cochran Q and Degrees of Freedom

In Table XIII.7, site-specific associations between SMC and dementia are summarised. In contrast to findings for cognitive function in participants without dementia, the positive associations were strong and significant in all sites with lower levels of between-site heterogeneity and these largely driven by the very strong associations in the Chinese sites. Adjustments did not alter associations substantially or consistently.

Table XIII.7 – Unadjusted and adjusted OR (95% CI) for the independent effect of any dementia diagnosis on Subjective Memory Complaints prevalence.

Site	Model 1	Model 2	Model 3
Cuba	**2.79 (2.17-3.59)**	**2.86 (2.19-3.73)**	**3.31 (2.36-4.63)**
Dominican Republic	**1.98 (1.48-2.64)**	**1.88 (1.39-2.54)**	**1.74 (1.25-2.43)**
Peru (urban)	**2.30 (1.47-3.61)**	**2.10 (1.31-3.36)**	**1.81 (1.06-3.07)**
Peru (rural)	**4.58 (2.16-9.74)**	**3.99 (1.81-8.79)**	**3.79 (1.62-8.88)**
Venezuela	**5.54 (3.71-8.28)**	**4.41 (2.83-6.86)**	**3.84 (2.28-6.45)**
Mexico (urban)	**3.48 (2.24-5.41)**	**3.07 (1.90-4.97)**	**3.03 (1.78-5.18)**
Mexico (rural)	**2.59 (1.62-4.15)**	**2.28 (1.38-3.76)**	**1.98 (1.15-3.41)**
China (urban)	**8.22 (4.42-15.3)**	**7.24 (3.84-13.7)**	**6.19 (2.94-13.0)**
China (rural)	**70.0 (31.8-154)**	**57.2 (24.6-133)**	**27.3 (9.78-76.3)**
India (urban)	**2.99 (1.81-4.93)**	**2.98 (1.77-5.00)**	**3.76 (2.03-6.97)**
India (rural)	**2.73 (1.70-4.37)**	**2.59 (1.60-4.20)**	**2.55 (1.37-4.77)**
Pooled meta analysis			
Combined estimate	**3.22**	**2.99**	**2.83**
Test for overall effect	**(2.84-3.65)**	**(2.61-3.41)**	**(2.42-3.31)**
Heterogeneity Q	**90.97**	**70.92**	**39.11**
DF	**10**	**10**	**10**
p value	**<0.000**	**<0.000**	**<0.000**
I^2 Higgins	**89%**	**86%**	**74%**
(95% CI)	**(82-93)**	**(77-92)**	**(54-86)**

Model 1 = Unadjusted
Model 2 = Adjusted for age, gender and education.
Model 3 = Adjusted for age, gender, education, assets, living alone, depression, need of care and disability.
OR= Odds Ratio, **CI=** Confidence Interval

XIII.4 Discussion

In what is likely to be the largest analysis of subjective and objective cognitive function, the following were key findings:

Within the combined sample, associations with SMC were largely consistent with observations from other studies (to be discussed further below): in particular, strong associations with female gender, depression, and worse general health (e.g. disability).

Within the combined sample, there were significant and reasonably strong associations between SMC and worse cognitive function. These associations were comparable in strength between the four tests.

SMC prevalence was particularly low in Chinese sites (6.6% rural, 25.3% urban) and ranged from 31-46% in the remaining samples. SMC prevalence in participants with dementia ranged from 45-74%.

Associations between SMC and lower cognitive function in participants without dementia showed high levels of heterogeneity between sites. The strongest associations were found in the Chinese sites for all four tests with Indian sites tending to have the weakest associations. Overall strengths of association with SMC remained significant similar for the four tests in pooled analyses. Between-site heterogeneity was also similar between tests.

Associations between SMC and dementia were significant after adjustment in all sites. Between-site heterogeneity was high with strongest association in the Chinese sites. In contrast to findings for cognitive function, associations with dementia in India were similar in strength to those in the Latin American sites.

Key strengths of these analyses were the large numbers of community residents recruited, the heterogeneity and diversity of countries surveyed the well-characterized samples, the systematic and standardized definition of SMC, and characterization of depression and dementia using standard criteria. The measure of SMC requires particular consideration. As discussed in Chapter V, definitions of this construct have varied considerably between studies and there is no agreed standard definition. We therefore adopted a pragmatic

approach, deriving it from questions in the GMS instrument and applying an identical cut-off to that used in (to our knowledge) all other studies using the GMS for this purpose(Kim et al., 2011, Stewart et al., 2001a). An advantage is that the GMS is widely applied in international studies, allowing ease of replication in other cohorts. The SMC construct itself also has similarities to definitions applied in other settings – i.e. a complaint of poor memory and an indication that it is frequent and/or noticeable to the participant. However, severity was not directly assessed, nor was the precise nature of the complaint. Because SMC is by definition a symptomatic construct, there is no 'gold standard' against which to establish criterion validity (i.e. whether someone complaining of poor memory is truly experiencing this). Associations with objective cognitive function and dementia will be considered below. A further potential methodological weakness is that we analysed SMC as defined by the subject participating in the study without addressing the memory report from relatives or caregivers; however, these issues will be considered further in Ch XIV.

Considering the overall prevalence, this was 33.5% for the combined sample and, with the exception of the prevalence in the rural site in China (6.5%), the range within the remaining sites was from 25.3% to 45.5%. This is very similar to the range reported in Jonker's review of community based studies (25-50%) (Jonker et al., 2000). A key advantage over estimates derived from reviews was that the measure of SMC was identical in all sites and the sampling approaches were comparable, although as mentioned previously, individual sites cannot be assumed to be nationally representative. Participation rates were also relatively high for all sites. A key finding was therefore that there is an appreciable prevalence range even if SMC criteria and sampling are harmonised to what is likely to be the most feasible extent.

In addition to the comparable prevalence range, associations between SMC and contextual variables in the sample as a whole were also comparable to those observed in previous research from other populations. We confirmed, for example, in the combined samples, associations of SMC with age, gender and poverty reported by several authors. In our study an increase in the frequency of SMC was noted among older (aged 75 years and over) participants (OR 1.33, 95% CI 1.24-1.43), female participants (OR 1.37, 1.47-1.28) and participants with less than three household assets (OR 1.24, 1.12-1.37). As summarized in Chapter V, most studies have reported an increase in subjective memory problems in older subjects (Bassett and Folstein, 1993, Blazer, 1997, Gagnon et al., 1994, Jonker, 1996, Jonker et al., 2000) and among females (Gagnon et al., 1994, Jonker, 1996, O'Connor et al., 1990). Associations with educational attainment have been less consistent in the literature and in our unadjusted and un-stratified analyse we found no evidence for a clear trend. Depression has almost universally been found to be associated with SMC in previous research, as previously summarized, and a strong relationship was found in the pooled samples.

The primary objective for the analyses discussed in this chapter was to clarify associations between SMC, cognitive function and dementia and to describe the consistency of these between sites. While some community samples of older people have revealed associations between memory complaints and memory impairment (Jonker et al., 2000), these findings are controversial as others have not found associations (Jonker et al., 2000, Mitchell, 2008, Stewart et al., 2001a, Trouton et al., 2006). Specifically within samples without dementia, a significant association was found between self-reported memory problems and poor memory performance in two studies (Bassett and Folstein, 1993, Blazer, 1997) independent of the level of depressive symptoms. In our study the participants with lowest cognitive

functioning had the highest prevalences of SMC, although with substantial and significant between-site heterogeneity as will be discussed further below.

Interestingly associations between SMC and lower cognitive function when meta-analysed across the samples were very similar in strength whether the test was measuring global function, verbal fluency, immediate or delayed recall, with fully adjusted odds ratios weakest for delayed recall and verbal fluency (both combined estimates 1.19), followed by global function (1.25), with the strongest being for immediate word list recall (1.28). The weaker associations may reflect psychometric 'distance' from the specific complaint (i.e. for verbal fluency) and/or limitations in the measurement applied (i.e. delayed recall being measured only on a 10-point scale). A limitation imposed by the practical aspects of the 10/66 programmes was that the cognitive assessments were inevitably limited in domains and depth, the primary purpose being to establish dementia prevalence rather than more subtle neuropsychological deficits. Established cross-cultural applicability is also limited for many assessments.

Dementia has been found to be associated with memory complaints in several previous community surveys (Jonker et al., 2000, Trouton et al., 2006, Bolla et al., 1991, Jonker, 1996), and we found strong and significant associations between SMC and dementia in all sites. In general, therefore, the 'accuracy' of SMC as a complaint was confirmed – i.e. overall, people with worse cognitive function were more likely to report it as a problem, at least in response to questions on memory. Given that the associations were cross-sectional, it is possible that the participants were responding particularly to the test environment (i.e. reporting SMC because they were aware they had performed relatively poorly). However, in the standard 10/66 schedules the questions on SMC are administered quite some time

after any cognitive assessments and reporting bias is unlikely. An important methodological point to note in this respect is that SMC items within the GMS schedule have negligible influence on the AGECAT algorithm output (M Dewey – personal communication) and so play no role in the 10/66 dementia diagnosis.

A striking feature of the findings was their heterogeneity between sites. The Chinese sites exhibited the most consistent variations from the norm in this respect and require particular consideration. In particular, SMC prevalence was most rare in these samples, particularly the rural site, but its prevalence in people with dementia was highest – hence the strongest odds ratios between SMC and dementia. These findings were supported by consistent results for cognitive function in those without dementia where associations with SMC were also strongest in China. The results therefore indicate a higher level of 'accuracy' in some settings compared to others. One possible explanation for heterogeneity is that there are other competing influences on SMC as a symptom, or willingness to report it, besides actual level of cognitive function. In settings such as those in China, these 'competing causes' may be absent or have less influence so that cognitive complaints, when they do occur are more likely to represent worse underlying cognitive function. Other variation between sites was less substantial and less consistent. For associations with cognitive function, the weakest associations tended to be found in the two Indian sites. However, the same was not true for associations with dementia where the weakest associations were found in Dominican Republic, urban Peru and rural Mexico. This may reflect differences in thresholds at which cognition is noted to be problematic – potentially less for India compared to other sites.

XIV. – INFORMANT-REPORTED MEMORY DEFICITS PREVALENCE AND CORRELATES

XIV. 1 Introduction.

As described in Chapter VI, the current knowledge is limited on how informant-reported memory deficits (IMDs) relate to memory self-appraised by the participant themselves and their measured cognitive functioning. Nevertheless, IMDs, as an alternative to subjective deficits, are becoming integral to the MCI construct. In community-based dementia studies, researchers have often combine the approaches to augment the discriminating ability of dementia although previous studies have found that informant reports perform as well as cognitive assessments (Law and Wolfson, 1995; Hall et al., 1996; Mackinnon and Mulligan, 1998; Cacchione et al., 2003; Knafelc et al., 2003; Mackinnon et al., 2003; Tierney et al., 2003; Slavin et al., 2010). The aims of the analyses described in this chapter were to describe and compare IMD prevalence and associations (particularly with cognitive function) in the 10/66 samples.

XIV. 2 Method

XIV. 2.1 Sample

The samples were as described in Chapter X.

XIV. 2.2 Measures

The following measures were used in these analyses; they refer to characteristics of the participant unless stated otherwise:

1. For this analysis we considered the following participant characteristics as independent variables: age, gender, education level (previously defined groups), household assets, living status (alone or not), subjective memory complaint (as defined in Chapter XIII) cognitive functioning (CSI-D cog-score, verbal fluency, immediate and delayed recall categorized as

defined in Chapter XIII), GMS depression, 10/66 or DSM-IV dementia, need for care reported by the informant and disability (WHODAS).

2. IMD was ascertained using the 26-item informant interview (CSI-D 'relscore'), which enquires about the participant's daily functioning and overall health status. The questions are derived originally from the Cambridge Examination for Mental Disorders (CAMDEX) (Roth et al., 1986; Hendrie et al., 1988) and the Blessed Dementia Scale (Morris et al., 1993). The CSI-D informant interview includes questions about changes in the index participant's activities of daily living. However, the informant is first asked to evaluate whether or not there have been any memory problems in the participant using the following 6 questions:

1. Does he/she forget where he/she has put things?

2. Does he/she forget where things are usually kept?

3. Does he/she forget the names of friends?

4. Does he/she forget members of the family?

5. Does he/she forget when he/she last saw you?

6. Does he/she forget what happened the day before?

The optional responses are: no', 'sometimes' and 'yes' which are scored as 0, 0.5 and 1, respectively. The 7 items were summed to create an IMD score (0-7; referred to as informant memory score hereafter), with higher scores indicating worse memory function, and for this analyses a binary category was arbitrarily created on the basis of a score of >=2 and < 2 to define IMD.

XIV. 2.3 Statistical Analysis

Analyses were carried out on the 10/66 data archive release 2.6, using STATA version 10.1 (STATA, 2007). Global prevalence (combined samples) of IMD stratified by age group,

gender, educational level, assets, living alone, depression, dementia, need of care, disability, and cognitive functioning, was reported with ORs (95% CI) calculated for between-group comparisons. The crude prevalence stratified by site was then described for the whole samples, and then for those with and without dementia. Logistic regression analyses were used to investigate unadjusted and adjusted associations between IMD and independent variables using three models: 1) unadjusted; 2) adjusted for age, gender and education; 3) adjusted additionally for assets, living alone, depression, need of care and disability. For separate analyses, SMC and dementia were entered as binary variables and measures of cognitive functioning (CSI-D cog-score, verbal fluency (animal naming), immediate and delayed recall (CERAD)) in participants without dementia were entered in defending quartile groups. To determine overall associations, outputs from the eleven-study site were combined into fixed effect meta-analyses estimating the degree of heterogeneity using Cochrane Q and Higgins' I^2 (95% CI) (Higgins JP, 2002) tests.

XIV.3 Results

Unadjusted associations between participant characteristics and IMD are summarized in Table XIV.1. Significant associations were found between higher IMD prevalence and older age, female gender, higher number of assets, depression, dementia, disability and need for care. Significant associations were also found with lower cognitive function and SMC. Highest risk was found in the group with some rather than no education at all; however, there was no consistent trend across the other education groups.

Further descriptions of IMD prevalence are described in Table XIV.2. The overall IMD prevalence was 29.2% in the combined sample, although varied widely among the sites from 7.8% in rural India to 38.1% in Dominican Republic. The IMD prevalence was lowest

in both Indian sites followed by the Chinese sites, with a more homogeneous 28-38% range for the Latin American sites. Ranges in participants without dementia followed a comparable pattern between sites. Those in participants with dementia ranged from 71-93% in China and Latin America, with lowest prevalences of 19% and 61% in rural and urban Indian sites respectively.

Table XIV.1. Prevalence of informant-reported memory deficit (IMD) stratified by participant characteristics.

Variable	Categories	Total	% IMD	OR (95%IC)
Age (years)	65-74	8,853	24.4	1
	75+	6,152	36.1	1.75 (1.63-1.88)
Gender	Male	5,724	25.0	1
	Female	9,248	31.6	1.39 (1.29-1.49)
Education	None	3,197	25.4	1
	Some	3,913	34.2	1.52 (1.37-1.69)
	Completed primary	4,282	28.5	1.17 (1.05-1.30)
	Completed secondary	2,263	26.5	1.06 (0.93-1.20)
	Completed tertiary	1,280	28.6	1.17 (1.01-1.36)
Number of assets	3 or less	2,111	23.5	1
	More than 3	12,893	30.2	1.40 (1.26-1.56)
Living alone	No	13,872	29.3	1
	Yes	1,150	27.7	0.92 (0.80-1.05)
Depression	No	14,123	27.9	1
	Yes	899	56.6	2.66 (2.32-3.04)
Dementia	No	13,643	24.1	1
	Yes	1,379	79.9	12.5 (10.9-14.4)
Need for care	No	13,233	25.3	1
	Yes	1,415	61.3	4.68 (4.18-5.24)
Disability (WHODAS) score	Below 90th percentile	13,488	26.5	1
	90th percentile or above	1,381	53.7	3.22 (2.88-3.60)
Global cognitive functioning	Quartile 4	3,754	18.3	1
	Quartile 3	3,732	23.9	1.40 (1.25-1.57)
	Quartile 2	3,768	30.3	1.94 (1.74-2.17)
	Quartile 1	3,768	44.3	3.55 (3.19-3.95)
Verbal fluency	Quartile 4	3,007	21.7	1
	Quartile 3	4,328	24.7	1.18 (1.06-1.32)
	Quartile 2	3,547	31.0	1.63 (1.45-1.82)
	Quartile 1	4,140	37.9	2.21 (1.98-2.46)
Immediate recall	Quartile 4	3,272	19.1	1
	Quartile 3	3,255	24.5	1.37 (1.22-1.55)
	Quartile 2	4,553	29.2	1.74 (1.56-1.95)
	Quartile 1	3,937	41.6	3.01 (2.70-3.37)
Delayed Recall	Quartile 4	2,569	19.7	1
	Quartile 3	4,700	25.0	1.36 (1.20-1.53)
	Quartile 2	2,609	24.9	1.35 (1.18-1.55)
	Quartile 1	5,144	40.0	2.72 (2.42-3.05)
Subject memory complaint	No	9,831	19.8	1
	Yes	4,945	46.2	3.47 (3.22-3.75)

IMD= Informant Reported Memory Deficit , **OR=** Odds Ratio, **IC=** Confidence Interval, **WHO-DAS=** World Health Organization - Disability Assessment Schedule, **ICD=** International Classification Disease

Table XIV.2. Prevalence of informant-reported memory deficit (IMD) by site and dementia status

Site	With dementia		Without dementia		Total sample	
	Number with IMD	IMD prevalence (%)	Number with IMD	IMD prevalence (%)	Number with IMD	IMD prevalence (%)
Cuba	323	93.2	2,621	26.8	2,944	34.0
Dominican Rep	242	86.0	1,769	31.5	2,011	38.1
Peru Urban	130	86.2	1,251	28.1	1,381	33.6
Peru Rural	36	75.0	516	25.0	552	28.3
Venezuela	145	91.7	1,820	26.9	1,965	31.7
Mexico Urban	93	85.0	910	32.8	1,003	37.6
Mexico Rural	87	75.9	913	31.2	1000	35.1
China Urban	84	82.1	1,076	19.0	1,160	23.5
China Rural	56	71.4	946	8.8	1002	12.3
India Urban	75	61.3	930	13.9	1,005	17.4
India Rural	108	19.4	891	6.4	999	7.8
Total	**1,379**	**79.9**	**13,643**	**24.1**	**15,022**	**29.2**
log likelihood model1		-8481.9579		-536.75528		-7178.829
log likelihood model 2		-8732.3558		-614.73165		-7380.8507

IMD= Informant reported Memory Deficit, **LR=** Likelihood ratio

Logistic regression analyses for the association between IMD and SMC in participants without dementia are summarized in Table XIV.3. Odds ratios remained significant and relatively unaltered by adjustment across all sites. Associations in most sites were within a relatively small range (e.g. fully adjusted odds ratios from 2.0 to 3.4) apart from the two Chinese sites, particularly the rural sample, where these were substantially stronger.

Table XIV.3 – Logistic regression analyses of the associations between subjective memory complaint (SMC) and informant-reported memory deficit (IMD) in participants without dementia.

Site	Odds ratio (95% CI) for the association between IMD and SMC		
	Model 1	Model 2	Model 3
Cuba	3.22 (2.68-3.88)	3.26 (2.70-3.93)	3.40 (2.75-4.20)
Dominican Republic	3.12 (2.52-3.86)	3.01 (2.42-3.74)	2.66 (2.12-3.33)
Peru (urban)	2.50 (1.94-3.24)	2.46 (1.90-3.20)	2.33 (1.78-3.04)
Peru (rural)	3.66 (2.42-5.55)	3.68 (2.37-5.71)	3.73 (2.39-5.82)
Venezuela	3.69 (2.95-4.60)	3.52 (2.80-4.41)	3.41 (2.67-4.37)
Mexico (urban)	2.06 (1.53-2.76)	2.07 (1.54-2.79)	2.00 (1.48-2.72)
Mexico (rural)	2.31 (1.72-3.10)	2.18 (1.62-2.93)	2.22 (1.63-3.02)
China (urban)	4.82 (3.46-6.73)	5.00 (3.55-7.05)	4.82 (3.39-6.86)
China (rural)	14.6 (7.16-29.8)	14.9 (7.06-31.2)	11.4 (4.74-27.3)
India (urban)	3.02 (2.07-4.41)	2.93 (2.00-4.29)	2.91 (1.91-4.43)
India (rural)	2.36 (1.34-4.17)	2.30 (1.31-4.06)	3.01 (1.34-6.79)
Pooled meta analysis			
Combined estimate	3.11 (2.85-3.39)	3.05 (2.79-3.33)	2.95 (2.69-3.24)
Test for overall effect			
I^2 Higgins (95% CI)	77% (58-87)	77% (59-87)	71% (46-84)

Model 1 = Unadjusted

Model 2 = Adjusted for age, gender and education.
Model 3 = Adjusted for age, gender, education, assets, living alone, depression, need of care and disability.
IMD= Informant reported Memory Deficit, **SMC=** Subjective Memory complaints, **CI=** Confidence Interval

Logistic regression analyses of associations between IMD and the four tests of cognitive function in participants without dementia are summarized in Tables XIV.4-7. Pooled associations were strongest for global function (CSI-D cog-score) and weakest for immediate recall, although within a small range (fully adjusted pooled ORs 1.15 to 1.28). However, significant between-site heterogeneity was again observed – highest for verbal fluency, lowest for delayed recall. In general, associations were strongest in the two Chinese sites (particularly the rural sample) and consistently weakest in the two Indian sites. Associations in rural Peru were weak for global function and verbal fluency but relatively strong for the two recall tasks.

Table XIV.4 – Site-specific associations between lower global cognitive function and informant-reported memory deficit (IMD) in participants without dementia

Site	Odds ratio (95% CI) for IMD per descending quartile of CSI-D cog-score		
	Model 1	Model 2	Model 3
Cuba	1.29 (1.18-1.40)	1.26 (1.14-1.39)	1.36 (1.22-1.52)
Dominican Republic	1.32 (1.19-1.45)	1.25 (1.12-1.40)	1.20 (1.07-1.35)
Peru (urban)	1.05 (0.92-1.20)	0.99 (0.85-1.15)-	0.92 (0.79-1.08)
Peru (rural)	1.56 (1.27-1.91)	1.43 (1.14-1.79)	1.41 (1.11-1.79)
Venezuela	1.44 (1.29-1.60)	1.49 (1.31-1.69)	1.40 (1.23-1.59)
Mexico (urban)	1.14 (1.00-1.31)	1.19 (1.02-1.39)	1.17 (1.00-1.37)
Mexico (rural)	1.37 (1.17-1.60)	1.34 (1.13-1.59)	1.34 (1.13-1.60)
China (urban)	1.54 (1.28-1.85)	1.83 (1.47-2.28)	1.62 (1.28-2.04)
China (rural)	2.31 (1.85-2.89)	2.20 (1.75-2.76)	2.03 (1.58-2.60)
India (urban)	1.07 (0.89-1.28)	1.08 (0.86-1.36)	1.10 (0.87-1.38)
India (rural)	1.22 (0.80-1.86)	1.07 (0.61-1.88)	1.05 (0.59-1.88)
Pooled meta analysis			
Combined estimate Test for overall effect	1.32(1.26-1.37)	1.31(1.25-1.37)	1.28(1.22-1.35)
I^2 Higgins (95% CI)	81%(68-89)	81%(67-89)	77%(58-87)

Model 1 = Unadjusted

Model 2 = Adjusted for age, gender and education.

Model 3 = Adjusted for age, gender, education, assets, living alone, depression, need of care and disability.

IMD= Informant Reported Memory Deficit, **CSI-D=** Community Screening Interview for Dementia, **CI=** Confidence Interval

Table XIV.5 – Site-specific associations between lower verbal fluency and informant-reported memory deficit (IMD) in participants without dementia

Site	Odds ratio (95% CI) for IMD per descending quartile of verbal fluency (animal naming)		
	Model 1	Model 2	Model 3
Cuba	1.25 (1.15-1.36)	1.22 (1.11-1.34)	1.25 (1.13-1.39)
Dominican Republic	1.14 (1.03-1.27)	1.07 (0.96-1.19)	1.04 (0.93-1.16)
Peru (urban)	1.05 (0.93-1.19)	0.99 (0.86-1.14)	0.96 (0.83-1.11)
Peru (rural)	1.14 (0.92-1.42)	1.01 (0.80-1.26)	0.96 (0.76-1.22)
Venezuela	1.18 (1.05-1.31)	1.19 (1.06-1.34)	1.15 (1.02-1.29)
Mexico (urban)	1.17 (1.01-1.35)	1.20 (1.03-1.40)	1.20 (1.02-1.41)
Mexico (rural)	1.10 (0.95-1.28)	1.06 (0.91-1.24)	1.05 (0.90-1.23)
China (urban)	2.70 (2.21-3.31)	2.98 (2.41-3.69)	2.87 (2.30-3.57)
China (rural)	1.24 (1.02-1.51)	1.14 (0.92-1.41)	1.10 (0.88-1.37)
India (urban)	0.82 (0.60-1.11)	0.79 (0.57-1.08)	0.74 (0.53-1.03)
India (rural)	1.54 (1.06-2.25)	1.48 (0.98-2.21)	1.40 (0.92-2.12)
Pooled meta analysis			
Combined estimate Test for overall effect	1.21 (1.16-1.26)	1.17 (1.12-1.23)	1.15 (1.01-1.21)
I^2 Higgins (95% CI)	87%(79-92)	89%(83-93)	89%(82-93)

Model 1 = Unadjusted

Model 2 = Adjusted for age, gender and education.

Model 3 = Adjusted for age, gender, education, assets, living alone, depression, need of care and disability.

IMD= Informant reported Memory Deficit, **CI=** Confidence Interval

Table XIV.6 – Site-specific associations between lower immediate recall and informant-reported memory deficit (IMD) in participants without dementia

Site	Odds ratio (95% CI) for IMD per descending quartile of immediate recall (CERAD word list)		
	Model 1	Model 2	Model 3
Cuba	1.30 (1.20-1.42)	1.27 (1.16-1.39)	1.29 (1.17-1.43)
Dominican Republic	1.30 (1.18-1.45)	1.28 (1.15-1.43)	1.22 (1.09-1.37)
Peru (urban)	1.20 (1.06-1.37)	1.21 (1.05-1.39)	1.18 (1.02-1.36)
Peru (rural)	1.05 (0.85-1.30)	0.94 (0.74-1.19)	0.93 (0.73-1.18)
Venezuela	1.21 (1.09-1.35)	1.27 (1.14-1.42)	1.23 (1.09-1.38)
Mexico (urban)	1.12 (0.97-1.29)	1.17 (1.00-1.36)	1.16 (0.99-1.36)
Mexico (rural)	1.25 (1.07-1.45)	1.25 (1.07-1.47)	1.27 (1.08-1.49)
China (urban)	1.81 (1.55-2.11)	2.08 (1.76-2.47)	1.94 (1.63-2.30)
China (rural)	2.32 (1.66-3.24)	2.17 (1.52-3.10)	2.02 (1.41-2.90)
India (urban)	1.11 (0.94-1.32)	1.14 (0.94-1.38)	1.14 (0.93-1.40)
India (rural)	1.59 (0.84-3.01)	1.48 (0.77-2.82)	1.39 (0.72-2.66)
Pooled meta analysis Combined estimate Test for overall effect	1.28(1.23-1.33)	1.29(1.23-1.35)	1.27(1.21-1.33)
I^2 Higgins (95% CI)	77%(59-87)	80%(65-89)	75%(55-86)

Model 1 = Unadjusted

Model 2 = Adjusted for age, gender and education.

Model 3 = Adjusted for age, gender, education, assets, living alone, depression, need of care and disability.

IMD= Informant reported Memory Deficit, **CERAD=** Consortium to establish a registry for Alzheimer Disease, **CI=** Confidence Interval

Table XIV.7 – Site-specific associations between lower delayed recall and informant-reported memory deficit (IMD) in participants without dementia

	Odds ratio (95% CI) for IMD per descending quartile of delayed recall (CERAD word list)		
Site	**Model 1**	**Model 2**	**Model 3**
Cuba	1.18 (1.08-1.28)	1.13 (1.04-1.24)	1.16 (1.05-1.28)
Dominican Republic	1.34 (1.21-1.48)	1.33 (1.20-1.49)	1.30 (1.16-1.45)
Peru (urban)	1.19 (1.05-1.34)	1.18 (1.03-1.35)	1.17 (1.02-1.34)
Peru (rural)	1.02 (0.84-1.24)	0.92 (0.74-1.14)	0.91 (0.73-1.14)
Venezuela	1.08 (0.98-1.20)	1.13 (1.01-1.25)	1.10 (0.99-1.23)
Mexico (urban)	1.12 (0.98-1.28)	1.16 (1.01-1.33)	1.15 (1.00-1.33)
Mexico (rural)	1.20 (1.05-1.38)	1.20 (1.04-1.38)	1.21 (1.05-1.40)
China (urban)	1.69 (1.42-2.00)	1.86 (1.56-2.24)	1.67 (1.38-2.03)
China (rural)	1.98 (1.45-2.72)	1.80 (1.30-2.49)	1.82 (1.30-2.56)
India (urban)	1.01 (0.85-1.20)	1.02 (0.84-1.24)	1.04 (0.86-1.27)
India (rural)	1.15 (0.80-1.64)	1.08 (0.74-1.57)	1.04 (0.71-1.52)
Pooled meta analysis Combined estimate Test for overall effect	1.20(1.15-1.25)	1.20(1.45-1.25)	1.19(1.14-1.24)
I^2 Higgins (95% CI)	76%(57-87)	77%(60-87)	68%(39-83)

Model 1 = Unadjusted
Model 2 = Adjusted for age, gender and education.
Model 3 = Adjusted for age, gender, education, assets, living alone, depression, need of care and disability.
IMD= Informant Reported Memory Deficit, **CERAD=** Consortium to establish a registry for Alzheimer Disease, **CI=** Confidence Interval

Logistic regression analyses of associations between IMD and dementia status are summarized in Table XIV.8. The two were statistically significant and strongly associated in all sites, the strongest associations being in Cuba (OR 27.4 in the fully adjusted model) and the weakest in rural India (fully adjusted OR 2.4). Again, adjustments did not have a substantial impact on the strengths of association and between-site heterogeneity was high.

Table XIV.8 – Site-specific associations between dementia and informant-reported memory deficit (IMD)

Site	Odds ratio (95% CI) for IMD and dementia		
	Model 1	**Model 2**	**Model 3**
Cuba	37.5 (24.1-58.4)	34.1 (21.5-53.9)	27.4 (16.5-45.3)
Dominican Republic	13.3 (9.03-19.5)	11.8 (7.97-17.4)	11.2 (7.38-16.8)
Peru (urban)	15.9 (9.56-26.4)	14.2 (8.37-24.1)	13.2 (7.28-23.8)
Peru (rural)	9.00 (4.10-19.7)	7.89 (3.33-18.7)	6.04 (2.44-15.0)
Venezuela	30.1 (16.5-54.8)	34.1 (17.1-67.6)	24.8 (12.2-50.6)
Mexico (urban)	11.6 (6.38-21.0)	11.4 (6.08-21.3)	9.46 (4.88-18.3)
Mexico (rural)	6.93 (4.14-11.6)	5.84 (3.43-9.94)	5.31 (3.05-9.25)
China (urban)	19.7 (11.1-34.8)	23.0 (12.7-42.0)	13.9 (6.72-28.8)
China (rural)	26.0 (14.0-48.3)	24.9 (12.8-48.7)	11.4 (5.21-24.9)
India (urban)	9.85 (5.84-16.6)	10.5 (6.04-18.1)	10.3 (5.78-18.4)
India (rural)	3.53 (2.01-6.21)	3.43 (1.87-6.29)	2.37 (1.28-4.41)
Pooled meta analysis Combined estimate Test for overall effect	14.1 (12.0-16.6)	13.4 (11.4-15.9)	10.5 (8.78-12.6)
I^2 Higgins (95% CI)	84%(74-91)	84%(72-90)	80%(65-89)

Model 1 = Unadjusted
Model 2 = Adjusted for age, gender and education.
Model 3 = Adjusted for age, gender, education, assets, living alone, depression, need of care and disability.
OR= Odds Ratio, **CI=** Confidence Interval

XIV.4 Discussion

The key findings from this analysis were as follows:

IMD in the combined samples was associated with similar participant characteristics to SMC, namely increased age, female gender, depression, need for care and disability. Like SMC, there was no clear association with higher or lower education levels. Unlike SMC it was more common in participants who had more rather than less assets.

The prevalence of IMD was more than threefold higher in participants with dementia compared to those without. It was also associated with lower cognitive function in the combined samples, to a similar extent with all four cognitive tests, and with SMC.

In participants without dementia, IMD was significantly and independently associated with SMC in all sites and with lower cognitive function in most sites. Both associations were stronger in the Chinese sites, particularly in rural China and associations with cognitive function were weak or absent in Indian sites. The odds ratios were similar between cognitive tests.,

Significant associations were found between IMD and dementia in all sites but there was evidence of significant and high between-site heterogeneity with a markedly weaker association in rural India.

As has been highlighted previously, key strengths of this analysis were the large sample sizes, the community samples with high response rates, the heterogeneity and diversity of countries surveyed spread across five world regions, and the characterization of the sample,

allowing adjustments for key measures of social and health status, including diagnostic assessments of depression and dementia. The definition of IMD was made *a priori* and had face validity, derived as it was from a well-used schedule with established cross-cultural applicability. However, there is yet to be a standard definition of IMD to apply in epidemiological research and findings can only therefore be viewed as preliminary and un-replicated. Unlike SMC, a key limitation with IMD as applied here is that the CSI-D informant interview is a core component of the dementia diagnostic assessment, so that associations with dementia are inevitably circular and may be more reflective of the performance of the algorithm between sites than illustrating a feature of dementia *per se*. However, the same is likely to be the case in any epidemiological study of dementia since a history of cognitive decline is a core component in all-standard diagnostic systems and informants are a key source of that information in the absence of longitudinal cognitive data. This circularity should not; however, be an issue regarding any other measure particularly since the informant was not usually present at the participant interview (particularly in those without dementia) and so would be unaware of the cognitive performance and/or responses to SMC questions. As highlighted in Chapter XIII, cognitive assessments were limited in scope because of the logistics of the study and availability of cross-culturally applicable assessments. Although reliability of the IMD measure was not formally evaluated, rigorous quality control monitoring was in place to maximize consistency across sites. Furthermore, the questions were relatively straightforward ones administered verbatim to informants. Finally, any loss of reliability would more likely introduce non-differential measurement error – i.e. bias true associations to the null and obscure rather than exaggerate them.

In the combined samples, the prevalence of IMD was 29.2%. The Latin American sites had relatively consistent prevalences of around 30% (28.7- 38.1) with lower values observed in China (23.5 and 12.3%) and India (17.4% and 7.81%). Rural India had the lowest crude IMD prevalence not only within the total sample but also, following stratification, in groups with and without dementia. In the combined samples, we found associations of IMD with older age and gender. As described earlier, most studies have reported an increase in subjective memory problems in older subjects and in women. The association with educational attainment is less consistent in the literature and in this report we confirm these findings even when we were able to find a tendency of higher prevalence of SMC among the less educated subjects that participated in our study.

In terms of cognitive associations, those with dementia should be treated with caution as discussed earlier because of the incorporation of IMD within dementia diagnostic criteria (and within the 10/66 algorithm). However, taking this into account, the variation between sites is interesting – for example, the finding in the rural Indian site that in 80% of dementia cases the informant did not report the level of IMD that was present in over 90% of dementia cases in Cuba. However, in the absence of dementia, IMD remained significantly associated with SMC in all sites – i.e. reflecting participant and informant agreement about cognitive difficulties. To our knowledge, this association has not been assessed before in a large multicultural community population and clearly it has to be viewed as preliminary and in need of replication. It is possible that it may be stronger in cultures where there are close-knit families and where a complaint by one member is more likely to be noticed by another; however, the interrelationship between family members around perceived impairment in one of them has received little systematic evaluation, particularly at relatively early stages of cognitive impairment prior to dementia onset.

We also found associations between IMD and worse performance on objective tests of cognitive function by the index participant. In community samples of older people associations have been found between informant memory complaints and memory impairment. In the 10/66 sites, as with SMC, the strongest independent associations were observed for the measures of global function and immediate word list recall. Again, this may reflect a different domain measured in verbal fluency where impairment is less apparent to an informant. It is possible that the weaker association with delayed compared to immediate recall may reflect the same phenomenon – i.e. that deficient immediate recall is more evident to others than deficient delayed recall (possibly because of compensatory strategies available). Alternatively it may simply reflect the fact that immediate recall was measured on a 30-point scale and delayed recall on a 10-point scale.

As with associations reported for SMC in Chapter XIII, there was significant between-site heterogeneity in most associations. In rural China, the particularly strong associations between SMC and cognitive impairment or dementia reported in Chapter XIII were also observed in relation to IMD in these analyses. Although SMC in Indian sites had been weakly associated with cognitive function in the absence of dementia, associations with IMD were comparable in strength to those in Latin American countries. However, associations between IMD and cognitive function were similarly weak to those between SMC and cognitive function in the Indian sites. The pattern has differences to that between SMC and cognitive function in China – here, SMC was relatively uncommon but much more 'accurate' (assuming accuracy to reflect a strength of association with observed function), whereas in India IMD was both uncommon and 'inaccurate'. The competing cause hypothesis discussed in Chapter XIII for SMC and dementia/cognition in China

appears unlikely to be relevant here since higher numbers of competing causes of IMD accounting for a weak association with dementia in India would not explain the overall low prevalence. Similarly, a general lack of performance of IMD as a construct in India might account for a low prevalence but not for a specific lack of association with cognitive impairment. Instead, the picture is more consistent with a combination of reluctance to report the symptom in general and more marked reluctance in the case of someone with objective cognitive impairment – possibly because of stigma but equally possibly because of societal or familial compensatory mechanisms whereby someone with declining cognitive function may receive more support so that the impairment no longer becomes evident. However, these conclusions need to be viewed as speculative in the absence of more specific evidence.

XV. - COGNITION AND ACTIVITIES OF DAILY LIVING IMPAIRMENT

XV.1 Introduction

Functional disability in the elderly is defined as an acquired difficulty in performing basic everyday tasks or more complex tasks needed for independent living. According to this definition, functionality encompasses all body functions, tasks, or actions, and disability includes impairment, limited capacity, or restricted performance of activities (Pinheiro, 2009). Impairment in functioning is core to the distinction between MCI and dementia. The aims of the analyses described in this chapter were to investigate the prevalence of activities of daily living impairment (ADLI) and factors associated with this in the 10/66 samples, in particular investigating the relationship with cognitive function and heterogeneity in this between sites. ADLI was evaluated from informant reports.

XV.2 Method

XV.2.1 Sample

The samples were as described in Chapter X.

XV.2.1 Measurements

The following measures were used in these analyses:

1. For this analysis we considered the following participant characteristics: age, gender, education level (previously defined groups), number of assets, living alone status, depression (GMS) and dementia (as previously defined). For cognitive function, the same four measures were considered as previously described (CSI-D cog-score, verbal fluency (animal naming), immediate and delayed recall (CERAD word list)).

2. ADLI was ascertained using items of the informant interview from the Community Screening Instrument for Dementia (CSI-D) previously described. The decision to use this measure was guided by the following considerations: 1) Self-reported disability derived from participant interviews would be potentially problematic as an outcome analysed against cognitive function as an exposure, because of reporting bias; 2) A detailed analysis of the WHODAS outcome had already formed the basis for another PhD thesis (R Sousa, passed 2011) based on these samples. Six questions in the CSI-D informant interview concern the participant's daily functioning, enquiring about loss of function within six domains: household tasks, previous skill/hobby, handling money, feeding, dressing and toileting. Four of these (household tasks, feeding, dressing and toileting), require the interviewer to ascertain whether the problem or difficulty is caused by physical limitation (if the answer is yes to this, then the primary question is scored as 0). The questions are listed in full below:

1. DOES SHE/HE HAVE DIFFICULTY PERFORMING HOUSEHOLD CHORES THAT SHE/HE USED TO DO, SUCH AS PREPARING FOOD OR BOILING A POT OF TEA? IF YES - HOW OFTENDOESTHATHAPPEN?

    0 No

    1 Yes, Sometimes

    2 Yes, Regularly

1a. - Does the INTERVIEWER think that the problem is primarily due to physical disability? (CHORE/DIS)

    0 No, not due to physical disability

    1 Yes, due to physical disability

2. HAS THERE BEEN A LOSS OF A SPECIAL SKILL OR HOBBY SHE/HE COULD MANAGE BEFORE?

    0 No

    1 Yes

3. HAS THERE BEEN A CHANGE IN HER/HIS ABILITY TO HANDLE MONEY?

    0 No difficulty

    1 Some difficulty

    2 Cannot handle money

4. DOES SHE/HE HAVE DIFFICULTY FEEDING HERSELF?

    0 Eats cleanly with proper utensils

    1 Eats messily with a spoon only

    2 Simple solids such as biscuits

    3 Has to be fed

4a. – Does the INTERVIEWER think that the problem is primarily due to physical disability?

    0 No, not due to physical disability

    1 Yes, due to physical disability

5. DOES SHE/HE HAVE DIFFICULTY DRESSING?

    0 Dresses self

    1 Occasionally misplaces buttons etc.

    2 Wrong sequences, commonly forgets items

    3 Unable to dress

5a. - Does the INTERVIEWER think that the problem is primarily due to physical disability?

    0 No, not due to physical disability

1 Yes, due to physical disability

6. DOES SHE/HE HAVE DIFFICULTY USING THE TOILET? DOES SHE/HE WET OR SOIL HER/HIMSELF?

0 No problems

1 Occasionally wets bed

2 Frequently wets bed

3 Double incontinence

6a. - Does the INTERVIEWER think that the problem is primarily due to physical disability?

0 No, not due to physical disability

1 Yes, due to physical disability

The scoring for the '0/1/2' items was 0, 0.5 and 1 respectively. For the analyses described here, a binary category was created a *priori* where any score of 0.5 or greater was classified as ADLI.

Consideration was given as to whether or not to use measures of physical health as covariates. Following consultation, a decision was made not to do this for the following reasons: i) some physical disorders might have resulted as a consequence of cognitive decline, so that adjustment for these would have represented an 'overadjustment'; ii) physical disorders most likely to be confounders for reasons of their being risk factors for cognitive impairment, such as hypertension and diabetes, are not prime causes of population-levels of disability in older people; iii) physical disorders most likely to cause disability in older people at a population-level (e.g. musculoskeletal disorders) are not candidate risk factors for cognitive decline; iv) an exception to (ii) and (iii) is stroke,

although its relationship to cognitive decline is complex (with prospective studies indicated bidirectional causation) and it was not felt to have sufficient prevalence in the samples to be a major confounder (since information on subclinical cerebrovascular disease was not available); v) the informant-rated ADL outcome was specifically designed to focus on disability not clearly caused by physical disorders.

XV.2.3 Statistical Analysis

Analyses were carried out on the 10/66 data archive release 2.6, using STATA version 10.1 (Stata, 2000) and, broadly, followed the pattern adopted for SMC and IMD. Prevalence of ADLI was first calculated in the combined samples followed by stratification by age group, gender, educational level, assets, living alone, depression, dementia, and cognitive function (quartile groups) with odds ratios for group differences. The prevalence was next stratified by site and dementia status. Logistic regression analyses were used to further investigate site-specific associations between ADLI and the four tests of cognitive function in participants without dementia. The models used for these analyses were as follows:1) unadjusted; 2) adjusted by socio-demographic variables (age, gender, education) and 3) adjusted for the same model 2 variables plus other relevant variables (assets, living alone and depression). As described previously, the analysis outputs for the sites were combined using fixed effect meta-analyses estimating the degree of heterogeneity using Cochrane Q and Higgins' I^2 (95% CI) (Higgins JP, 2002) tests.

XV.3 Results

Associations between ADLI and participant characteristics in the combined samples are described in Table XV.1. Significant associations were found with older age, female gender,

and fewer assets, as well as with dementia, depression, and lower cognitive function on all four tests. No significant associations were found with education or living alone.

Table XV.1. Prevalence of activities of daily living impairment (ADLI) stratified by participant characteristics.

Variable	Categories	Number	ADLI (%)	OR (95%CI)
Age groups	65-74	8,853	10.0	1
	75+	6,152	22.8	2.66(2.42-2.92)
Gender	Female	9,248	15.6	1.12(1.02-1.22)
	Male	5,724	14.2	1
Education	None	3,197	16.8	1.44(1.19-1.75)
	Some	3,913	18.8	1.65(1.37-1.99)
	Primary	4,282	13.6	1.13(0.93-1.36)
	Secondary	2,263	10.2	0.81(0.65-1.00)
	Tertiary	1,280	12.3	1
Number of assets	3 or less	2,111	19.1	1.38(1.22-1.56)
	more than 3	12,893	14.6	1
Living alone	No	13,872	15.2	1
	Yes	1,150	16.4	1.09(0.93-1.29)
Depression	No	14,123	13.7	1
	Yes	899	39.6	4.13(3.59-4.76)
Dementia	No	13,643	9.8	1
	Yes	1,379	69.3	20.8(18.3-23.7)
Global cognitive functioning	Quartile 4	3,754	4.8	1
	Quartile 3	3,730	8.0	1.74(1.43-2.10)
	Quartile 2	3,763	13.3	3.04(2.54-3.64)
	Quartile 1	3,775	34.7	10.5(8.93-12.4)
Verbal fluency	Quartile 4	3,007	5.9	1
	Quartile 3	4,328	9.5	1.67(1.39-2.00)
	Quartile 2	3,547	16.4	3.11(2.60-3.71)
	Quartile 1	4,140	27.1	5.89(4.98-6.97)
Immediate recall	Quartile 4	3,272	5.5	1
	Quartile 3	3,255	8.1	1.50(1.24-1.83)
	Quartile 2	4,553	13.3	2.63(2.21-3.13)
	Quartile 1	3,937	31.5	7.91(6.69-9.34)
Delayed Recall	Quartile 4	2,569	5.8	1
	Quartile 3	4,700	8.7	1.54(1.26-1.87)
	Quartile 2	2,609	11.1	2.01(1.63-2.47)
	Quartile 1	5,144	28.0	6.28(5.25-7.50)

ADLI= Activities of Daily Living, **OR=** Odds Ratio

The ADLI prevalence in the combined samples was 15.2% and varied considerably among the sites from 3.5% in urban India to 25.9% in Dominican Republic (Table XV.2). A particularly large difference in ADLI prevalence was observed between the rural and urban sites in India (24.4 vs. 3.5 respectively). Prevalence's in participants with dementia ranged from 28.0% in urban India to 86.4% in Cuba while the prevalence in participants without dementia ranged from 1.1% in rural China to 19.4% in Dominican Republic.

Table XV.2. Prevalence of activities of daily living impairment by site and dementia status

Site	With dementia		Without dementia		Total sample	
	Number with ADLI	ADLI prevalence (%)	Number with ADLI	ADLI prevalence (%)	Number with ADLI	ADLI prevalence (%)
Cuba	323	86.4	2,621	7.8	2,944	16.4
Dom. Rep.	242	73.6	1,769	19.4	2,011	25.9
Peru (urban)	130	76.9	1,251	6.3	1,381	13.0
Peru (rural)	36	36.1	516	5.8	552	7.8
Venezuela	145	80.0	1,820	10.3	1,965	15.5
Mex. (urban)	93	74.2	910	15.7	1,003	21.1
Mex. (rural)	87	46.0	913	9.9	1000	13.0
China (urban)	84	78.6	1,076	3.0	1,160	8.5
China (rural)	56	51.8	946	1.1	1002	3.9
India (urban)	75	28.0	930	1.5	1,005	3.5
India (rural)	108	40.7	891	22.5	999	24.4
Total	**1,379**	**69.3**	**13,643**	**9.8**	**15,022**	**15.2**

ADLI= Activities of Daily Living

Logistic regression analyses for associations between ADLI and cognitive functioning in participants without dementia are summarized in Tables XV.3-6. Considering the combined estimates, adjustment for covariates had only modest effects on associations with ADLI and all remained significant after adjustment. However, the association of ADLI with global function (CSI-D cogscore) was over twice as strong as that with delayed recall, the other two tests occupying intermediate positions. Site-specific associations between worse global function and ADLI were statistically significant in five sites, whereas worse delayed recall was only significantly associated with ADLI in two sites.

Between-site heterogeneity was strongest for verbal fluency and immediate recall. Across all four tests, the sample from the urban China site had substantially stronger associations between cognition and ADLI than the remainder, with the rural China sample occupying second position for all tests apart from verbal fluency. Otherwise, there was no clear consistency in site ranking across the four assessments although they tended to be relatively strong in Venezuela and were consistently significant in Cuba.

Table XV.3 – Site-specific associations between lower global cognitive function and activities of daily living impairment (ADLI) in participants without dementia

	Odds ratio (95% CI) for ADLI per descending quartile of CSI-D cog-score		
Site	**Model 1**	**Model 2**	**Model 3**
Cuba	1.38(1.20-1.59)	1.27(1.08-1.50)	1.26(1.06-1.49)
Dominican Republic	1.57(1.39-1.77)	1.52(1.33-1.73)	1.45(1.27-1.66)
Peru (urban)	1.27(1.02-1.58)	1.22(0.93-1.59)	1.11(0.85-1.44)
Peru (rural)	1.48(0.98-2.25)	1.47(0.95-2.28)	1.39(0.86-2.24)
Venezuela	1.88(1.58-2.23)	1.77(1.46-2.16)	1.63(1.34-1.99)
Mexico (urban)	1.31(1.10-1.57)	1.27(1.04-1.56)	1.25(1.03-1.53)
Mexico (rural)	1.26(1.01-1.57)	1.22(0.96-1.55)	1.22(0.96-1.55)
China (urban)	3.69(2.52-5.41)	4.03(2.44-6.63)	3.70(2.22-6.18)
China (rural)	2.39(1.29-4.44)	2.07(1.08-3.96)	1.80(0.81-3.97)
India (urban)	1.51(1.03-2.20)	1.38(0.74-2.59)	1.44(0.69-3.00)
India (rural)	0.89(0.73-1.10)	0.75(0.58-0.96)	0.94(0.71-1.25)
Pooled meta analysis Combined estimate Test for overall effect	1.45(1.36-1.54)	1.37(1.28-1.47)	1.35(1.26-1.45)
I^2 Higgins (95% CI)	84% (73-91)	81% (68-89)	67% (38-83)

Model 1 = Unadjusted
Model 2 = Adjusted for age, gender and education.
Model 3 = Adjusted for age, gender, education, assets, living alone, depression.
ADLI= Activities of Daily Living, **CI=** Confidence Interval, **CSI-D=** Community Screening Interview for Dementia

Table XV.4 Site-specific associations between lower verbal fluency and activities of daily living impairment (ADLI) in participants without dementia.

	Odds ratio (95% CI) for ADLI per descending quartile of verbal fluency score		
Site	**Model 1**	**Model 2**	**Model 3**
Cuba	1.48(1.28-1.70)	1.40(1.21-1.63)	1.39(1.20-1.62)
Dominican Republic	1.20(1.07-1.36)	1.12(0.99-1.27)	1.10(0.97-1.24)
Peru (urban)	1.30(1.03-1.64)	1.26(0.98-1.64)	1.22(0.95-1.58)
Peru (rural)	1.31(0.86-1.99)	1.20(0.80-1.81)	1.10(0.74-1.64)
Venezuela	1.60(1.39-1.84)	1.51(1.29-1.77)	1.52(1.30-1.78)
Mexico (urban)	1.29(1.07-1.54)	1.21(0.99-1.47)	1.19(0.98-1.45)
Mexico (rural)	1.05(0.84-1.31)	1.03(0.82-1.29)	1.02(0.81-1.29)
China (urban)	2.55(1.85-3.52)	2.56(1.80-3.62)	2.48(1.73-3.56)
China (rural)	0.91(0.53-1.58)	0.78(0.39-1.59)	0.74(0.33-1.65)
India (urban)	0.48(0.26-0.90)	0.39(0.20-0.76)	0.39(0.19-0.80)
India (rural)	0.85(0.69-1.07)	0.82(0.65-1.03)	0.75(0.58-0.97)
Pooled meta analysis Combined estimate Test for overall effect	1.30(1.23-1.38)	1.23(1.15-1.31)	1.21(1.14-1.29)
I^2 Higgins (95% CI)	83% (71-90)	81% (69-90)	82% (69-90)

Model 1 = Unadjusted
Model 2 = Adjusted for age, gender and education.
Model 3 = Adjusted for age, gender, education, assets, living alone, depression.
ADLI= Activities of Daily Living, **CI=** Confidence Interval

Table XV.5 – Site-specific associations between lower immediate recall and activities of daily living impairment (ADLI) in participants without dementia

Site	Odds ratio (95% CI) for ADLI per descending quartile of CERAD word list immediate recall score		
	Model 1	Model 2	Model 3
Cuba	1.48(1.28-1.70)	1.40(1.21-1.63)	1.36(1.17-1.59)
Dominican Republic	1.20(1.07-1.36)	1.12(0.99-1.27)	1.12(0.98-1.27)
Peru (urban)	1.30(1.03-1.64)	1.26(0.98-1.64)	1.46(1.14-1.87)
Peru (rural)	1.31(0.86-1.99)	1.20(0.80-1.81)	1.00(0.60-1.65)
Venezuela	1.60(1.39-1.84)	1.51(1.29-1.77)	1.30(1.09-1.54)
Mexico (urban)	1.29(1.07-1.54)	1.21(0.99-1.47)	1.03(0.85-1.24)
Mexico (rural)	1.05(0.84-1.31)	1.03(0.82-1.29)	0.94(0.72-1.23)
China (urban)	2.55(1.85-3.52)	2.56(1.80-3.62)	3.86(2.57-5.81)
China (rural)	0.91(0.53-1.58)	0.78(0.39-1.59)	2.25(0.98-5.17)
India (urban)	0.48(0.26-0.90)	0.39(0.20-0.76)	0.84(0.44-1.62)
India (rural)	0.85(0.69-1.07)	0.82(0.65-1.03)	1.20(0.86-1.68)
Pooled meta analysis Combined estimate Test for overall effect	1.40(1.31-1.49)	1.28(1.19-1.37)	1.23(1.15-1.34)
I^2 Higgins (95% CI)	84% (73-91)	81% (68-89)	79% (63-88)

Model 1 = Unadjusted
Model 2 = Adjusted for age, gender and education.
Model 3 = Adjusted for age, gender, education, assets, living alone, depression.
ADLI= Activities of Daily Living, **CERAD=** Consortium to establish a registry for Alzheimer Disease **CI=**Confidence Interval

Table XV.6 – Site-specific associations between lower delayed recall and activities of daily living impairment (ADLI) in participants without dementia

Site	Odds ratio (95% CI) for ADLI per descending quartile of CERAD word list delayed recall score		
	Model 1	Model 2	Model 3
Cuba	1.33(1.16-1.53)	1.23(1.06-1.43)	1.20(1.03-1.40)
Dominican Republic	1.26(1.11-1.42)	1.15(1.02-1.30)	1.11(0.98-1.26)
Peru (urban)	1.40(1.14-1.71)	1.31(1.03-1.67)	1.27(0.99-1.62)
Peru (rural)	1.14(0.77-1.67)	1.03(0.68-1.55)	1.01(0.66-1.54)
Venezuela	1.22(1.05-1.41)	1.12(0.96-1.32)	1.11(0.95-1.30)
Mexico (urban)	1.15(0.96-1.37)	1.05(0.88-1.27)	1.04(0.86-1.26)
Mexico (rural)	1.06(0.86-1.30)	0.99(0.80-1.24)	0.99(0.80-1.24)
China (urban)	3.17(2.29-4.39)	2.89(2.01-4.16)	2.69(1.84-3.93)
China (rural)	2.32(0.95-5.65)	1.96(0.80-4.79)	1.70(0.71-4.07)
India (urban)	1.27(0.79-2.05)	1.13(0.66-1.93)	1.18(0.66-2.13)
India (rural)	1.25(1.01-1.55)	1.21(0.97-1.50)	1.21(0.94-1.56)
Pooled meta analysis Combined estimate Test for overall effect	1.28(1.21-1.36)	1.18(1.11-1.25)	1.15(1.08-1.23)
I^2 Higgins (95% CI)	74% (52-86)	67% (39-83)	60% (22-79)

Model 1 = Unadjusted
Model 2 = Adjusted for age, gender and education.
Model 3 = Adjusted for age, gender, education, assets, living alone, depression.
ADLI= Activities of Daily Living,
CERAD= Consortium to establish a registry for Alzheimer Disease
CI= Confidence Interval

XV. 4. - Discussion

The following were key findings from these analyses:

Activities of daily living impairment (ADLI) in the participant, as reported by their informant, were present in 15% of the total sample and were associated with increased age, female gender and fewer assets, as well as with depression, dementia and lower cognitive function.

ADLI prevalence varied substantially between sites from 4% in urban India to 26% in Dominican Republic. Prevalence in participants with dementia also varied with relatively high (>75%) frequencies in Cuba (86%), Venezuela (80%), urban China (79%), urban Peru (77%) and relatively low frequencies in urban India (28%) and rural Peru (36%).

Associations between ADLI and worse cognitive function in participants without dementia were present in combined samples for all four tests although stronger for the test of global function compared to the other three. The most consistently strongest associations between cognitive function and ADLI were observed in urban China, Venezuela and Cuba.

As described before, key strengths were the sample sizes, the community assessments, the high response rates, the heterogeneity and diversity of countries surveyed and the diagnostic assessments of depression and dementia. ADLI was derived from an informant interview and therefore had some objectivity and independence from the cognitive measures (e.g. removing the problem of people with cognitive impairment finding it difficult to report their daily function). Although defined *a priori* and drawn from a standard schedule with previous cross-cultural application, it should be borne in mind that the psychometric properties of the scale and cut-off have not been formally assessed.

However, as with the IMD definition, the questions are relatively straightforward and unlikely to be misunderstood. ADLI as defined here was strongly associated with a participant-reported WHODAS score above the 90th percentile with an odds ratio of 8.58 (95% CI 7.63-9.66). Disability has been assessed with a wide variety of instruments in previous research but even when instruments contain the same items, they may differ in how they assess specific aspects of performing the task or the severity of limitation in performing the task. Finally, it is important to bear in mind that impaired activities of daily living is a core component of dementia diagnostic criteria so that associations with dementia (as with those between IMD and dementia) are inevitably circular – although ADLI is not an absolute requirement in the 10/66 dementia algorithm as is clear from the wide range of prevalences in the second column of Table XV.2.

Functional impairment has significant implications for older adults because of the potential step of institutionalization as an outcome, higher mortality rates, poorer underlying health status, poorer health outcomes, poorer quality of life and caregiver burden (Angel & Fisco, 2001; Winer et al 1990). However, most epidemiological evidence on disability comes from high income countries, despite the fact that around 10% of the world's population (650 million people) suffer a disability (UN, 2006) and 80% of these live in LMIC settings (UN 2006; Lancet 2009). Relationships between cognition and disability are potentially complex to elicit when categories such as dementia or MCI are applied because the presence or not of a given level of disability is used to define such categories. Nevertheless, a considerable body of research has examined the relationship between cognitive abilities and ADL/ADLI functional performance, with particular reference to older adults. Cognitive ageing studies have addressed the relationship of functional performance to different and

specific cognitive functions, and performance on various standardized psychometric measures for several mental functions (Marson D, 2006).

In our analyses of the combined samples, increased prevalence of ADLI was found in older participants, female participants and those with fewer assets. There are reasonably consistent findings of an increase in disability prevalence with increasing age (Grundy, 1999; Paul, 2007; Berlau, 2009) and higher prevalence in women compared to men (Berlau, 2009; Zhao, 2009; Gu, 2009). The complex inter-relationship between education and income and their strong associations with poor health and onset of disability has also been illustrated by several studies (Taylor, 2010; Herd, 2007; Zimmer, 2003; Meltzer, 2001). In our unadjusted analyses we only confirmed the association with lower income (if fewer assets can be considered as a proxy for this) with no clear linear trend across education groups.

The principal objectives in these analyses were to clarify relationships between cognitive function and ADLI in participants without dementia. In our study clear evidence was found of associations between ADLI and lower cognitive function for all four measures, strongest for global cognitive functioning. Several studies have examined the association between cognitive and functional decline in what is termed 'normal' ageing (Barberger-Gateu, 1999; Mortimer, 1992; Willis, 1992). These authors have concluded that changes in functional performance are not the direct result of advancing age *per se* but instead are linked to a concurrent decline in those cognitive abilities that underlie everyday task competence. Global mental status measures, particularly neuropsychological measures of executive function, have been found to account for a significant portion of the variance in ADL and IADL function. Taking a broader view, deficits in higher-order cognitive abilities have

been found to correspond with difficulty in performing complex tasks of everyday living even in the preclinical stages of dementia (Griffith, 2003). It is likely that the CSI-D cog-score scale is measuring a broader range of functions, which in combination are likely to be more predictive of daily functioning than lower scores on a specific test such as verbal fluency or learning.

It is important, however, to bear in mind that causality between cognitive function and ADLI is difficult to infer, even in prospective research, particularly because of the difficulties distinguishing the influence of cognition from wider individual and environmental contexts. Cerebrovascular disorders for example may cause cognitive impairment due to effects on higher brain function and general functional incapacity due to effects elsewhere in the brain – i.e. acting as a confounder with no direct link between the cognitive impairment and ADLI. Because of the limited scope for in-depth assessments in the 10/66 sites (e.g. no neuroimaging available), these processes cannot be excluded entirely, despite specific features of the CSI-D ADLI assessment to allow impairments caused principally by physical ill health to be excluded from consideration.

As well as individual factors, socio-cultural environments may also modify the relationship between cognition and ADLI. Substantial variations in strengths of association were found and it is interesting that the strongest associations were not in sites with the lowest ADLI prevalence (i.e. not, like SMC, representing a propensity to report the construct less often but more 'accurately'). Instead, the strongest associations between ADLI and cognitive impairment in participants without dementia tended to be seen in the sites where ADLI had the highest prevalences in participants *with* dementia. This suggests that there may be

features of these environments, which render both pre-dementia cognitive impairment and dementia itself more disabling.

XVI. – GENERAL DISCUSSION AND CONCLUSIONS.

One of the main achievements of the work of the 10/66 DRG is to have the opportunity to compare data obtained with a consistent, systematic and validated methodology between large multicultural samples from different regions and countries in the low and middle income world, the focus of this thesis being to investigate data and associations relevant to the MCI construct. An objective for the 10/66 programme overall was to standardize assessments as much as possible in order to gain a clearer idea of international variation and this advantage was utilised for the analyses described here. The fact that substantial heterogeneity remained in many circumstances suggests important variation in constructs underlying the definition.

We found clear differences in cognitive function and symptom distributions between the sites. Cognitive norms tended to be lowest in India and highest in China, which was confirmed in relation to aMCI prevalence where, within the range of prevalence's from the different sites, China (0.8%) and India (4.3%) were at the extremes, with the Latin American countries occupying the central ground. This is interesting considering that the Latin American countries share many cultural similarities to each other and clear differences compared to China and India.

However, considering SMCs, these were relatively low in China, consistent with the higher norms and lower aMCI prevalence, but Indian prevalences were similar to those in Latin America. IMD on the other hand was low in both China and India compared to Latin America. The likelihood is that aMCI prevalence is primarily determined by cognitive function distributions within a given population, although it remains important to be aware

that the other elements of the construct may have more pronounced cultural influences. Low SMC and IMD prevalence may therefore have accounted at least in part for low aMCI prevalence in the Chinese sites but do not account for the relatively high aMCI prevalence in India.

Inconsistencies between sites in aMCI prevalence and in the constructs underlying the aMCI diagnosis support questions previously raised concerning its conceptual basis and/or operationalisation outside clinical settings. However, aMCI has been reported to be associated with increased mortality in prospective studies, and differences in aMCI associated to survival between country sites cannot be excluded as a factor influencing variation in prevalence. Longitudinal studies in these settings will contribute to clarify these questions.

Considering correlates of cognitive function we did not find consistent differences in demographic factors associated with cognition between sites. In the other hand SMC was particularly strongly related to both cognition and dementia in China. In the Indian sites, samples showed weak SMC associations with cognition, although those with dementia were similar to the Latin American range. IMD was more strongly associated with cognition in China and weaker in India compared to Latin America. IMD and SMC themselves were most strongly associated in China, but in India these were similar to associations in Latin America.

Taking the Chinese sites to begin with, and considering the relatively good cognitive function and low frequency of complaints or reported deficits (SMC/IMD) our findings suggest at least that 'accuracy' of these symptoms/reports may vary between settings, one possibility being that Chinese participants and informants were better able to identify genuine problems than those in other sites which could possibly be explained by them being less likely to report memory problems/deficits associated with other non-cognitive syndromes, therefore maximizing the specificity of the relationship with cognition. However, clearly this can only be a speculative conclusion and further more specific research is indicated. The impact of cognitive impairment may also be a factor and it is noteworthy that associations between cognitive test scores and ADLI in people without dementia were relatively high in urban China (to be discussed further below).

Considering the Indian sites, the picture is a little different because the associations between SMC and cognition in people without dementia were relatively weak but the associations between SMC and dementia were similar to those in Latin America. Also, IMDs were relatively weakly associated both with cognition and with dementia (but associations between IMD and SMC were comparable in strength to those in Latin America). As previously argued, it is possible that subjective complaints might have a different threshold between sites (i.e. in India, only become apparent in dementia and not in milder cognitive impairment) and that IMDs may be less reported in dementia, either because of reluctance to report this (e.g. because of stigma or social acceptability) or because there have been compensatory processes for reducing the visibility/impact of dementia so that informants do not even notice any deficit, although associations between cognition and ADLI were not markedly different in strength from those in many other sites.

Considering further potential differences in the impact of cognitive impairment, there was a relatively negative association between aMCI and WHODAS score in China but inferences are limited because of the self-report nature of the instrument.

Associations between aMCI in China and NPI symptoms seem to be particularly strong which again may reflect a rarer but more severe syndrome being identified; these findings are adding to others that are questioning us about the role of behavioural symptoms in early dementia stages, in some cases with evidence of earlier manifestations even than very subtle cognitive changes. Several recent studies have also reported that neuropsychiatric symptoms are present in 35-59% of individuals with MCI, with some of the more common symptoms being depression, anxiety, apathy, irritability, and problems with sleep (Feldman et al, 2004; Geda et al, 2004; Liketsos et al, 2002).

Considering ADLI, an important potential determinant of aMCI prevalence may be the threshold of 'impact' at which it is re-labeled as dementia. It is possible that low aMCI prevalence in a given setting may reflect a higher level of disability arising from cognitive impairment (for example because of a more demanding lifestyle for older people or lower social support) so that the 'window' between normal cognition and disabling cognitive impairment (i.e. dementia, according to standard definitions) is narrower. Some evidence was found for this in urban China where prevalence of ADLI was relatively high in people with dementia and the association relatively strong between cognition and ADLI in people without dementia.

Prevalence of ADLI on the other hand was relatively low in people from the urban Indian site, but strengths of association with cognitive function in the remainder were not

consistently weak relative to those in other sites. Although there are inconsistencies, the high between site heterogeneity found in this study suggests overall that the impact of cognitive impairment and/or dementia on ADLI varies to a meaningful extent between settings, which may have at least some influence on the prevalence and nature of a-MCI as a construct.

Further evaluation is needed of the associations with disability and neuropsychiatric symptoms since our findings do suggest higher than expected co morbidity and there are large absolute numbers of older people with aMCI in these rapidly ageing and populous world regions where the large number of those potentially affected has important implications in these rapidly ageing settings. However, little is known about the prevalence or impact of MCI in LAMIC settings; this is one of the first studies, to investigate the prevalence of a-MCI in LAMICs

We believe that this work has generated important findings that will produce a substantial impetus for further research in these regions. Follow-up has recently been completed in most 10/66 sites, which will provide further data on predictive validity. As has been mentioned, there are several potential implications for further research. A key limitation of the findings is that they are cross-sectional, whereas MCI constructs are envisaged to be primarily of longitudinal value as predictors of future dementia. The predictive validity of the aMCI categories therefore needs evaluating and comparing between sites. This will help clarify some of the variability identified in this thesis. For example, if aMCI has lower prevalence in China because the SMC/IMD components are restricting it to a more rare but more ‘accurate’ syndrome then incidence of dementia in participants with aMCI should be highest in China and lowest in India.

Prospective research is also indicated to investigate the onset of SMC/IMD in relation to different trajectories of cognitive decline as well as the temporal relationship between these two factors themselves (e.g. whether SMC identifies earlier or more mild deficits compared to IMD). Finally, the prospective relationship between cognitive decline and ADLI incidence could be further investigated in terms of the threshold at which function becomes impaired, the extent to which this varies between sites, and the extent to which any variation is accounted for by factors such as level of social support. As we previously mentioned, follow-up studies have recently been completed in the Chinese and Latin American 10/66 sites and data, as these become available, will be analysed with these objectives in mind.

For at least some assumed cultural variation, quantitative research is likely to provide only limited insights, and further exploration of underlying reasons for our observations is likely to require qualitative approaches. These could include in-depth studies into attitudes towards perceived memory deficits in older people (both by those reporting deficits and those concerned about deficits in a close other). The meaning of the symptoms/observations could be explored further, as could knowledge about dementia and attitudes towards help seeking from formal or informal sources. Of particular interest for the findings reported here would be research in China to clarify reasons for the relatively rare SMC and IMD categories including specific research in people reporting these symptoms/observations to understand further why these appear to be more accurate reflections of cognitive function than they are in other cultures, including Western settings.

In the meantime, while further research is awaited, there are certain implications which can be drawn for public health and clinical practice. First, it is important to bear in mind that MCI-related constructs applied in epidemiological research have differences to decisions made in clinical environments where there is more of a process of judgement regarding the presence and impact of cognitive impairment. Attempts to apply these in community studies have tended to lead to broader definitions with substantially lower predictive validity. Heterogeneity in prevalence has also been high and our study confirmed this, despite the standardisation of measurement and sampling across surveys.

Furthermore, there were clear and substantial variations in SMC, IMD and ADLI as important components of the syndrome. Regardless of underlying reasons, these at very least suggest important cultural or other environmental influences, so that community prevalences should be viewed with caution. Although the samples analysed are from particular international settings, some of the conclusions may be more generalisable. In particular, if differences between sites exist then differences between individuals may also be substantial in the same respects (e.g. ability / willingness to detect cognitive impairment in oneself or a close other, propensity for functional impairment at a given level of cognitive decline).

In clinical settings, the same issues apply where there is a focus on detection and management of MCI or early dementia. If some people in some settings or circumstances are more or less likely to notice/report memory deficits in themselves or others then services orientated around such reporting behaviour may have inevitable underlying inequalities in provision. The same may arise from differences in impacts of cognitive impairment if the impact itself is a component of a diagnosis and/or eligibility for

intervention. Clearly the findings from specific sites or countries need to be taken into account by local services (if only to seek replication and clarification through further research). However, the simple fact that context and environment have been found to be important in determining the associations of interest should be borne in mind much more widely.

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